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Formal Syntheses of Hirsutine and Rhynchophylline and Progress Toward the Enantioselective Total Synthesis of Citrinadin A

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Formal Syntheses of Hirsutine and Rhynchophylline and Progress Toward the Enantioselective Total Synthesis of Citrinadin A

by

Martin Youngjin Pettersson, B.S.

Dissertation

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of the Requirements

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Doctor of Philosophy

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Dedication

This dissertation is dedicated to my wonderful wife Julia who forever changed my life, and whose steadfast support and encouragement have made this challenging journey possible. It is also dedicated to our children Samuel and Anna who bring so much happiness into our lives.

Acknowledgements

I would like to thank my wife Julia for everything that she has done for me, and whose help and encouragement has made this work possible. I whish to thank my undergraduate research advisor Dr. David R. Williams, who inspired me to pursue a career in synthetic organic chemistry. I am particularly grateful to Dr. Stephen F. Martin for his guidance and support throughout graduate school, and I am also indebted to the current and former members of the S. F. Martin research group for all their help and friendship.

Formal Syntheses of Hirsutine and Rhynchophylline and Progress Toward the Enantioselective Total Synthesis of Citrinadin A

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Martin Youngjin Pettersson, Ph.D.

The University of Texas at Austin, 2007

Supervisor: Stephen F. Martin

The diastereoselective formal syntheses of the corynanthe alkaloid hirsutine and oxindole alkaloid rhynchophylline are described. The general approach features the use of ring-closing metathesis (RCM) to construct an α,β-unsaturated lactam, which is subjected to 1,4-addition. The lithium enolate of ethyl-1,3-dithiolane-2-carboxylate was identified as the optimal nucleophile in these systems. A key feature of this approach is that the stereochemical outcome of the 1,4-addition can be effectively controlled by appropriately sequencing the indole Boc-protection step to give either the C(3)-H/C(15)-H *cis* or C(3)-H/C(15)-H *trans* stereochemical relationship. As a result, we have developed a unified approach to both the "normal" and "pseudo" corynanthe alkaloids. This finding was highlighted through the synthesis of the complete carbon skeleton of the archetypal normal corynanthe alkaloid dihydrocorynantheol.

An efficient synthesis of the tricyclic spiroindolinone ABC-fragment of the marine alkaloid citrinadin A has been achieved. The synthesis relies on a novel asymmetric oxidative rearrangement of an indole to an oxindole using a chiral auxiliary

on the indole nitrogen to achieve facial selectivity. The transformation proceeds via the epoxidation of the indole C(2),C(3) double bond using DMDO, followed by a silica gel-mediated 1,2-epoxide rearrangement. Using this tactic, the spirooxindole of citrinadin A, which contains two adjacent quaternary centers, was formed in high yield and excellent diastereoselectivity. Efforts toward the fragment coupling of the tricyclic spiroindolinone with a 2,4,6-trisubstituted piperidine coupling partner are described.

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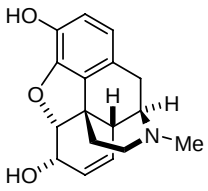
Chapter 1: Syntheses of Corynanthe, pseudo-Corynanthe and Oxindole Alkaloids

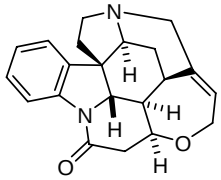
1.1 INTRODUCTION

For thousands of years nature has been an indispensable source of biologically active extracts from which important therapies have been derived. The extensive use of medicinal plants has been documented in the ancient Chinese, Egyptian and Native American civilizations, and to this day native tribes of the Amazon continue to use plants from the rain forest for the treatment of a variety of diseases.[1] It was not until 1805, however, that the first alkaloid was isolated in pure form. Sertürner's discovery of morphine (**1.1**) represented the start of a new era, not just of alkaloid isolation chemistry but of organic chemistry as a whole.[2] Along with morphine, perhaps the most well known alkaloids among the general public are strychnine (**1.2**) and quinine (**1.3**). The latter is readily available from the bark of the chinchona tree and was introduced to the Western civilization by South American Indians. Quinine has served as a ubiquitous treatment against malaria for over hundred years until the discovery of the synthetic drug chloroquine in the 1950's. However; with the steady rise of chloroquine resistant strains of malaria, quinine is again becoming increasingly important for the treatment of this devastating disease.

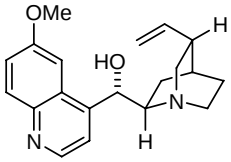
Figure 1.1



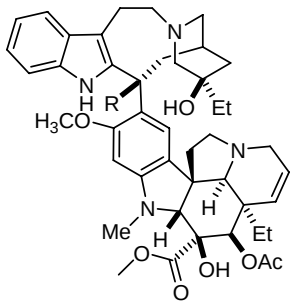
1.1



1.2



1.3



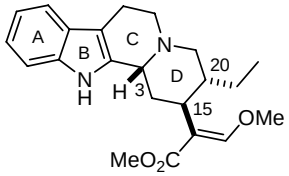
1.4 R = CO_2CH_3

Alkaloids have also found application in the treatment of cancer. The complex bis-indole alkaloid vinblastine (**1.4**) was first isolated from the Madagascar periwinkle, and after the initial discovery that **1.4** could effectively lower the count of white blood cells, Eli Lilly and Co. (Indianapolis, Indiana) began extensive biological evaluation of **1.4** and closely related alkaloids. It was eventually discovered that **1.4** is an effective treatment for Hodgkin lymphoma, for which it eventually was commercially developed.

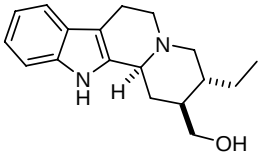
Aside from their biological relevance, several classes of alkaloids feature complex and fascinating molecular architectures, which pose significant challenges to practitioners of synthetic organic chemistry. Two such classes are the corynantheine-heteroyohimboid alkaloids and the closely related oxindole alkaloids (Figure 1.2). The latter is biogenetically related to the corynanthe alkaloids via an oxidative rearrangement of the indole unit. The corynanthe class can be further divided into four sub-groups differing in the stereochemical configurations of the substituents around the D-ring. These sub-groups are known as normal (C(3)-H α, C(15)-H α, C(20)-H β), pseudo (β, α, β), allo (α, α, α), epi-allo (β, α, α). For almost half a century, the corynanthe and oxindole alkaloids have served to inspire the development of new methodologies and synthetic strategies.[3]

Three such alkaloids, hirsutine (**1.5**) dihydrocorynantheol (**1.6**) and rhynchophylline (**1.7**) will be discussed in detail in this chapter.

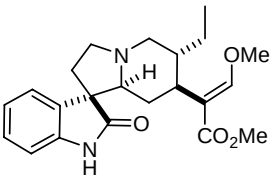
Figure 1.2



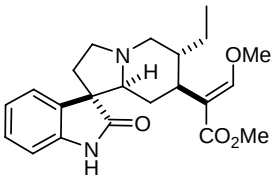
Hirsutine (**1.5**)



Dihydrocorynantheol (**1.6**)



Rhynchohylline (**1.7**)



iso-Rhynchohylline (**1.8**)

1.2 HIRSUTINE

1.2.1 Background

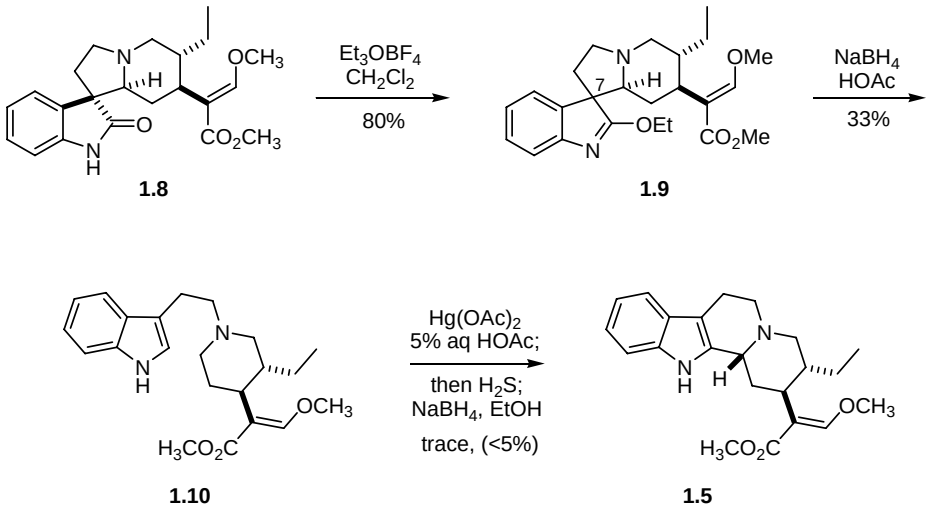
Hirsutine (**1.5**) is one of the corynanthe-type alkaloids of the "pseudo" sub-type possessing the characteristic C(3)-H β, C(15)-H α, C(20)-H β relative stereochemical configuration. It was first isolated by Shellard and co-workers in 1966 from the Asian plant *Mitragyna hirsuta Havil*.[4] Further work demonstrated that this alkaloid is present in a variety of *Mitragyna* and *Uncaria* species (Rubiaceae).[3] Corynanthe-type alkaloids represent one of the major constituents of the root bark of *Uncaria rhynchophylla* (Miq.), an important medicinal plant used in the Chinese "Kampo" medicine for the treatment of cardiovascular disorder such as hypertension with its symptoms of dizziness and headache. Hirsutine has more received increased attention due to the discovery by Takayama and co-workers that **1.5** possesses significant *in vitro* activity against the influenza A virus (subtype H3N2).[5] With EC_{50} = 0.4–0.57 μg/mL, **1.5** is approximately 11-20 times more potent than the clinically used ribavarin. The challenge of devising efficient strategies for controlling the stereochemistry around the D-ring coupled with the important biological activity of **1.5** has been the driving force behind a number of partial, formal, and total syntheses of **1.5** over the past four decades (*vide infra*).

1.2.2 Sakai's Partial Synthesis of Hirsutine (1972)

The first two syntheses of hirsutine (**1.5**) were both partial syntheses using other natural products as starting materials. In the early seventies, Sakai and co-workers investigated the conversion of oxindole alkaloids to their corresponding indole counterparts.[6] While the biomimetic oxidative rearrangement of indoles to oxindoles had

already been extensively studied by Finch and Taylor[7] the reverse transformation had not yet been reported. As shown in Scheme 1.1, Sakai and co-workers demonstrated that iminoethers such as **1.9**, which were readily obtained from the corresponding oxindoles (*iso*-rhynchophylline (**1.8**) in this case), could be reduced by $NaBH_4$ in acetic acid to afford 2,3-*seco*-indoles such as **1.10**. Interestingly, alkylation of the oxindoles with Meerwein salt resulted in epimerization of the C7-spirocenter, however, this was of no consequence since this stereocenter was destroyed in the ensuing reduction. The 2,3-seco-indoles were then subjected to an oxidative cyclization with $Hg(OAc)_2$ to afford the corresponding indoles in approximately 25%. However, in the case of hirsutine a complex mixture was obtained, and the natural product could only be isolated in trace amounts.

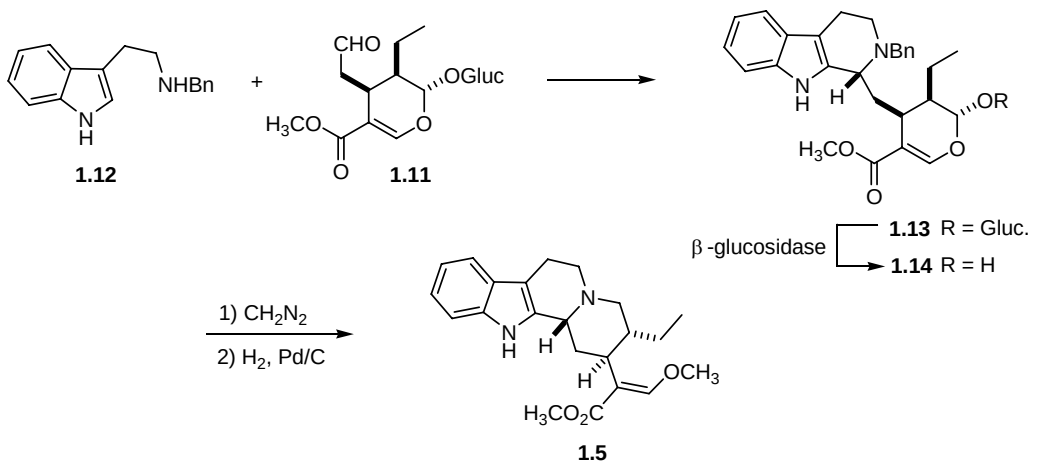
Scheme 1.1



1.2.3 Brown's Biomimetic Partial Synthesis of Hirsutine (1974)

The iridoid glucoside secologanine constitutes the biogenetic precursor to the vast majority of monoterpene indole alkaloids. This was exploited by Brown[8] in his biomimetic partial synthesis of hirsutine (**1.5**) and related alkaloids as depicted in Scheme 1.2. In this case, however, the dihydro analogue of secologanine **1.11** was employed, which underwent condensation with N^b-benzyltryptamine (**1.12**) to afford N^4-benzyl-18,19-dihydrovincoside (**1.13**). Following cleavage of the glucose group by the action of β-glucosidase to afford **1.14**, the synthesis of hirsutine was completed by subjecting **1.14** to diazomethane followed by hydrogenolysis. Hirsutine (**1.5**) was thus prepared in only four steps from dihydrosecologanine (**1.11**), although the yields and diastereomeric ratios were not reported.

Scheme 1.2

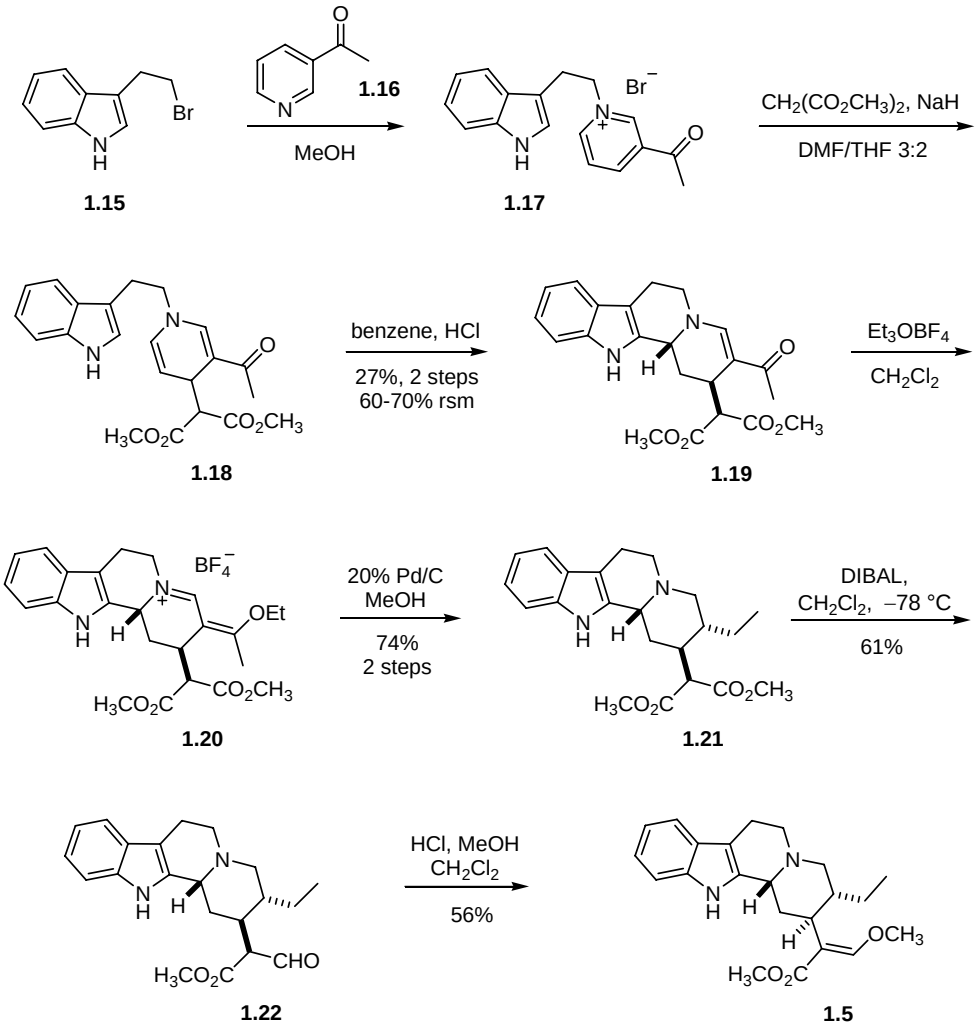


1.2.4 Wenkert's Racemic Total Synthesis of Hirsutine (1980)

The first total synthesis of hirsutine was accomplished by Wenkert[9] and co-workers. They developed an elegant and highly concise approach in which the first step involved the formation of a pyridinium salt by condensation of tryptophyl bromide (**1.15**) and pyridine derivative **1.16** (Scheme 1.3). The pyridinium ion **1.17** was then treated with the sodium enolate of dimethyl malonate to afford **1.18**, which was not isolated but immediately exposed to benzene saturated with hydrochloride gas to affect a cyclization that produced tetracycle **1.19**. While the yield was low for this transformation (27%), the majority of the unreacted starting material (60-70%) could be recovered and recycled. It is interesting to note that the cyclization of **1.18** proceeded in a regiospecific manner in spite of the fact that there are two enamines present in **1.18**. This can be explained by the fact that one of the olefins in **1.18** constitutes a vinylogous amide, which is much less acid sensitive and therefore less prone to undergo cyclization with the tethered indole. Following the cyclization, the vinylogous amide function of **1.19** was reduced in a two-step protocol commencing with *O*-alkylation with Meerwein salt followed by

hydrogenation of the tetrafluoroborate salt **1.20** to afford **1.21**. The total synthesis of **1.5** was then completed by partial reduction of the malonate with DIBAL followed by acid catalyzed methylation to form the vinylic carbonate of hirsutine. These last two transformations were used in several of the total syntheses of hirsutine that followed (*vide infra*).

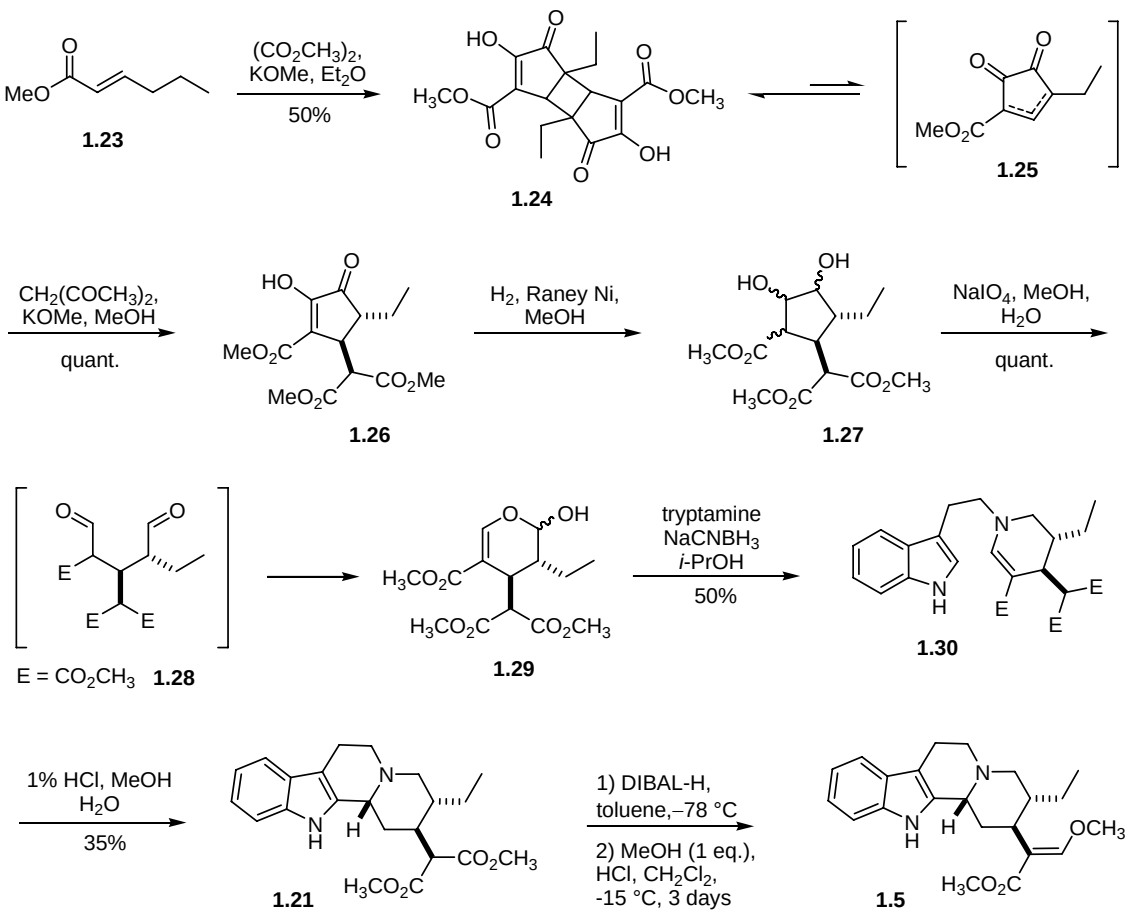
Scheme 1.3



1.2.5 Brown's Racemic Synthesis of Hirsutine (1984)

The main challenge in devising an efficient synthesis of the corynanthe alkaloids is to control the relative stereochemistry of the C3, C15 and C20 stereocenters around the D-ring. Brown and co-workers[10] envisioned accomplishing this task by setting the relative stereochemistry around a five-membered ring in which eclipsing 1,2-interactions would insure nearly complete diastereoselectivity. As depicted in Scheme 1.4 this would allow access to the synthetic dihydrosecologanine aglucone analogue **1.29**. Given the success in converting dihydro secologanine (**1.11**) into various indole alkaloids (*vide supra*) including hirsutine (**1.5**), Brown and co-workers anticipated an efficient entry into the corynanthe class of alkaloids via a synthetic analogue of **1.11**.

Scheme 1.4



Vinylogous Claisen condensation of hex-2-enoate (**1.23**) with dimethyl oxalate furnished the novel cylcopentene dimer **1.24** in 50% yield. This material exists in an equilibrium with cyclopentenone derivative **1.25**, which underwent a highly diastereoselective Michael addition when exposed to dimethylmalonate and triethylamine to provide **1.26** in quantitative yield as a single stereoisomer. Hydrogenation over Raney nickel afforded diol **1.27**, which was cleaved upon exposure to sodium periodate to furnish the secologanine analogue **1.29**. Reductive amination with tryptamine furnished **1.30** (50% yield), which was subjected to a one-pot ester hydrolysis/decarboxylation protocol followed by intramolecular stereoselective Pictet-Spengler reaction to afford

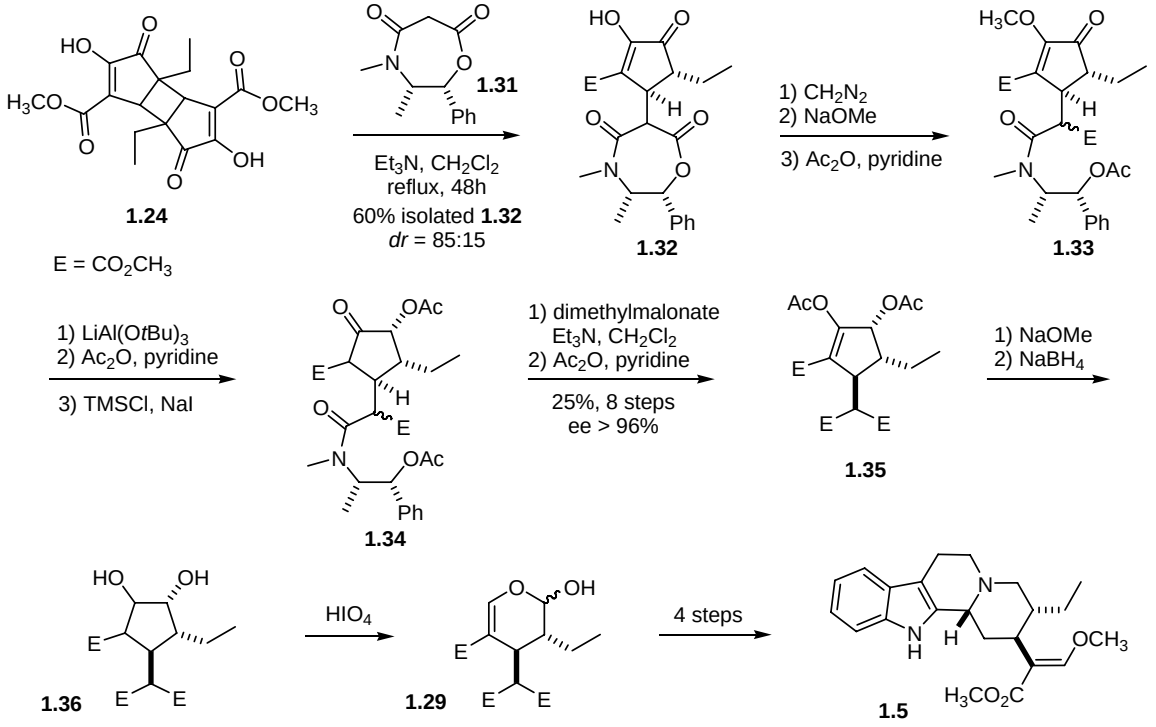
indoloquinolizidine **1.21** in 35% yield. The conversion of **1.21** to hirsutine (**1.5**) was accomplished using the procedure already described by Wenkert.[9] While the synthesis is rather concise, it is not readily adapted to an enantioselective synthesis. This issue was eventually addressed by Brown and co-workers about six years later, resulting in the first enantioselective synthesis of hirsutine (*vide infra*).

1.2.6 Brown's Enantioselective Synthesis of Hirsutine (1990)

Brown's approach to the asymmetric synthesis of hirsutine was to employ an chiral malonate equivalent in the form of the ephedrine derived oxazepine **1.31**. As depicted in Scheme 1.5, refluxing oxazepine **1.31** and cyclopentene dimer **1.23** in dichloromethane in the presence of triethylamine effected a thermodynamically controlled Michael addition, which set the two adjacent stereocenters on the cyclopentene ring with reasonable diastereoselectivity (85:15). After facile separation of diastereomers by silica gel chromatography, the desired isomer **1.32** could be isolated in 60% yield. With this material in hand, the researchers pressed forward toward the chiral secologanine analogue **1.29**. The oxazepine chiral auxiliary needed to be replaced with a malonate while retaining the fidelity of the two newly created stereocenters. In order to accomplish this goal, Brown first established that it was necessary to elaborate the Michael adduct **1.32** to **1.33**, in which the oxazepine had undergone ring-opening so as to render the cyclopentenone less sterically encumbered. Once the oxazepine ring had been opened, enone **1.33** could be reduced and further elaborated to **1.34** in preparation for the removal of the auxiliary. In the event, heating **1.34** in the presence of dimethylmalonate and triethylamine afforded cyclopentenone derivative **1.35** following acylation. This material was obtained in 25% yield over eight steps, and the enantiomeric excess was

found to be greater than 96%. Additionally, the auxiliary was easily recovered and recycled.

Scheme 1.5

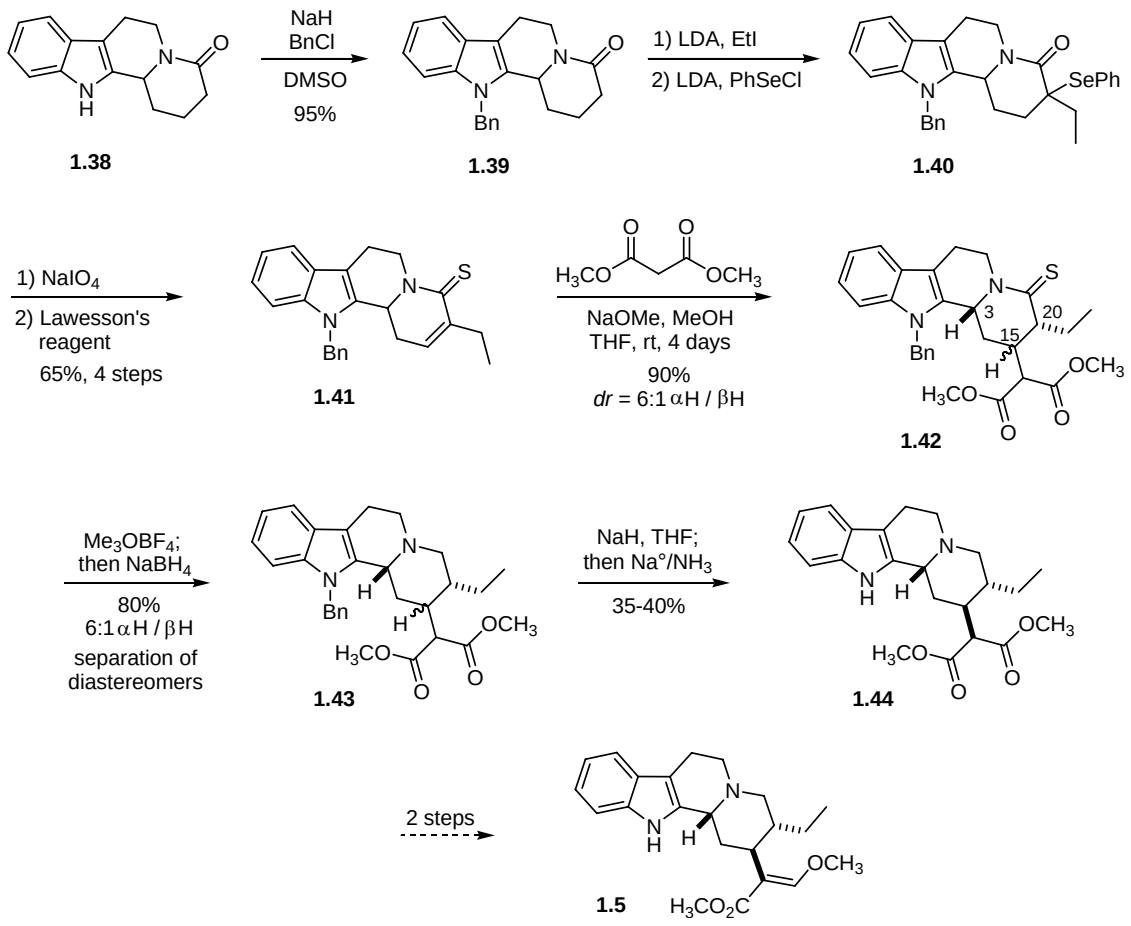


With cyclopentene derivative **1.35** in hand, only a few straightforward transformations remained to complete the synthesis of enantiopure dihydrosecologanine **1.29**. The completion of the first asymmetric synthesis of hirsutine (**1.5**) was then achieved using the same chemistry developed for the racemic synthesis. While the chiral asymmetric Michael addition is certainly an interesting tactic on its own merit, the drawback of its application to the asymmetric synthesis of hirsutine is that a rather long sequence of functional group transformations was required, resulting in a synthesis totaling 17 steps.

1.2.7 d'Angelo's Racemic Formal Synthesis of Hirsutine (1992)

The approach developed by d'Angelo[11] relied on a 1,4-addition to introduce the C(15) substituent on the D-ring. It had been established earlier that α,β-unsaturated lactams structurally related to **1.41** were not reactive toward 1,4-addition of dialkyl malonates,[12] and it was hypothesized that the conversion of the lactam to a thiolactam[13] would render it more susceptible toward 1,4-addition. Starting with the known indoloquinolizidine **1.38**,[14] a five step sequence furnished thiolactam **1.41** in good overall yield, setting the stage for the key 1,4-addition. The presence of the ethyl group in **1.41** significantly reduced its reactivity toward 1,4-addition with dimethylmalonate. As a result the reaction required four days at room temperature to go to completion, which stands in stark contrast to the des-ethyl analogue (not shown), which only required 5 hours. In spite of the poor reactivity, adduct **1.42** was obtained in 90% yield albeit as an inseparable mixture of C15 epimers (*dr* = 6:1). However, following desulfurization of the mixture, the two epimers **1.43** were readily separated by chromatography. The formal synthesis of **1.5** was then completed by removing the N-benzyl protecting group through dissolving metal reaction to afford **1.24** in a moderate yield of 35-40%. Indoloquinolizidine **1.24** had previously been converted to hirsutine (**1.5**) in two steps by Wenkert (*vide supra*). d'Angelo's approach to **1.44**, which was eight steps from **1.38** (nine steps from tryptamine), provides an interesting solution the problem of the poor reactivity of α,β-unsaturated lactams in 1,4-additions. It also represents one of the first successful applications of a 1,4-addition to introduce the C(15)substituent in corynanthe alkaloid synthesis.

Scheme 1.6



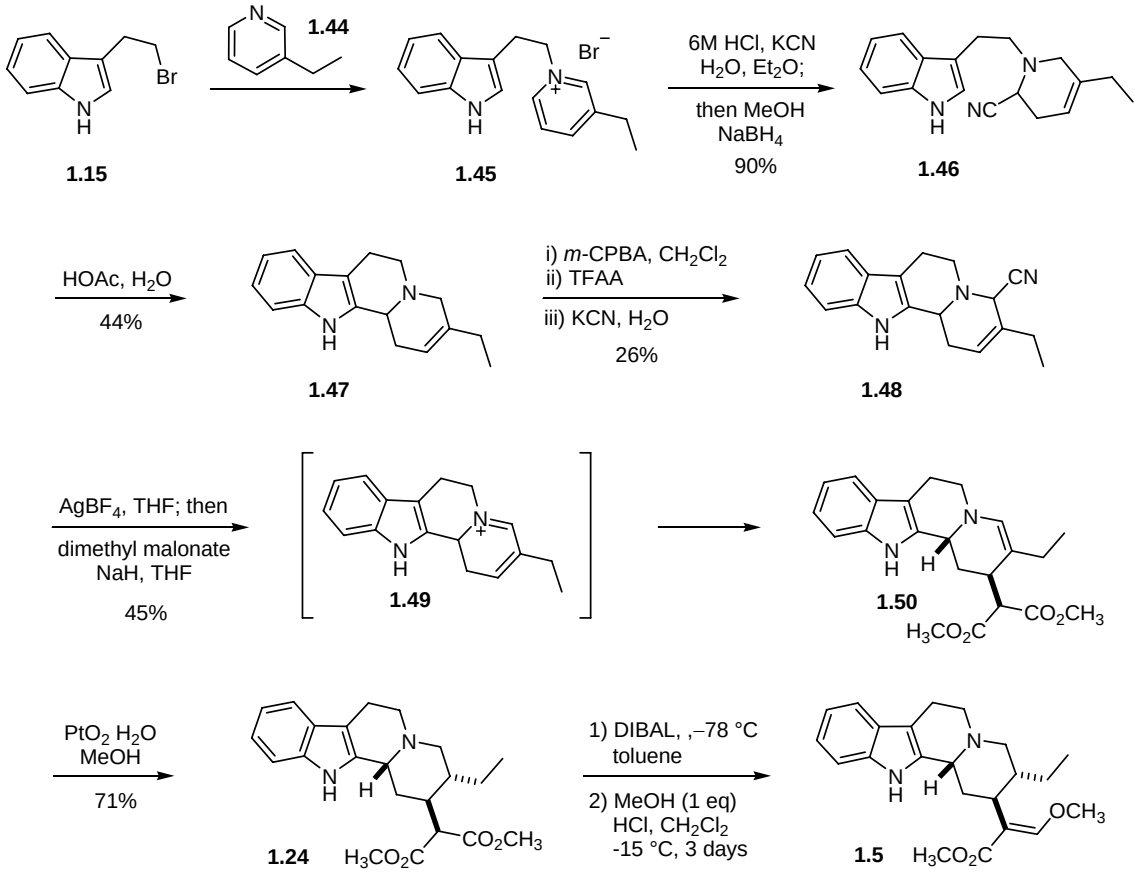
1.2.8 Lounasmaa's Racemic Synthesis of Hirsutine (1997)

In their ABD→ABCD approach to corynanthe alkaloids, Lounasmaa and co-workers utilized the addition of dimethylmalonate to a vinylogous iminium ion as a key step (Scheme 1.7).[15] The synthesis of the requisite substrate **1.48** commenced with the alkylation of 3-ethylpyridine (**1.44**) with tryptophyl bromide (**1.15**), and the resultant pyridinium ion was subjected to acid promoted addition of cyanide ion followed by reduction with sodium borohydride to afford **1.46** in good yield. Following acid-catalyzed cyclization, the resultant indoloquinolizidine **1.47** then underwent an

interesting three step, one-pot transformation. The tertiary nitrogen was first oxidized with *m*CPBA. The N-oxide intermediate thus formed was subjected to a modified Polonovski reaction by the addition of trifluoroacetic anhydride, which generated a conjugated iminium ion that was trapped in situ with cyanide ion to afford **1.48** in a modest yield of 26%. This modified Polonovski protocol was extensively studied,[16] and the regiochemistry of the iminium ion formation was found to be highly dependant on the nature of the substrate as well as on the specific reaction conditions used.

Exposure of **1.48** to $AgBF_4$ regenerated the conjugated iminium ion **1.49**, to which sodium dimethylmalonate was added in a 1,4-sense to afford **1.50** in a moderate yield (44%). Following stereoselective hydrogenation of the tertiary olefin of **1.50**, the synthesis was completed using the same endgame as described by Wenkert.[9] Lounasmaa's synthesis avoided the use of protecting groups, and it is only eight steps from tryptophyl bromide. However; the low yields associated with the modified Polonovski reaction and the key addition to the vinylogous iminium ion detracts somewhat from the overall elegance of this approach. Additionally, the diastereoselectivity of the vinylogous iminium reaction as well as the ensuing hydrogenation were not reported.

Scheme 1.7



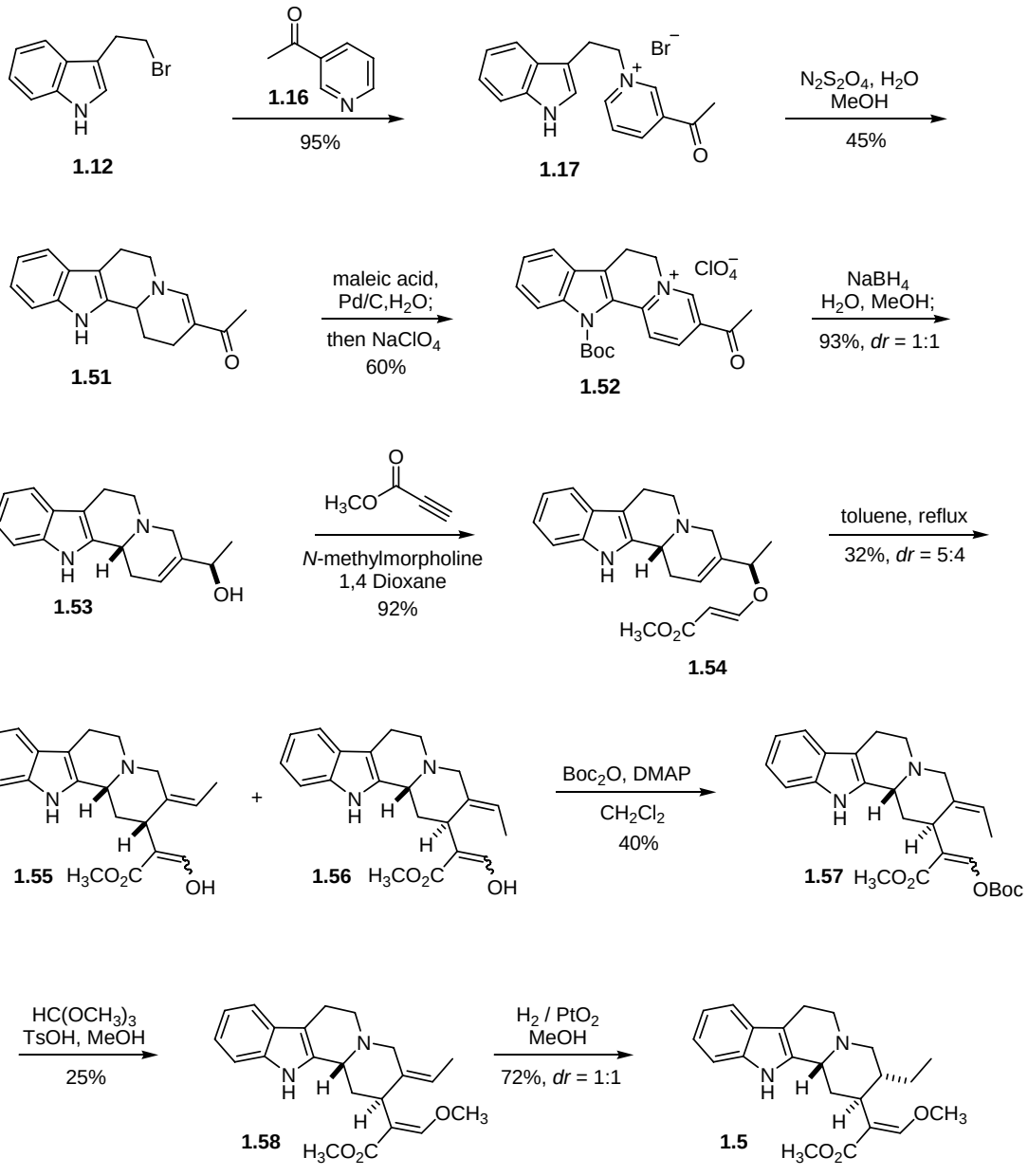
1.2.9 Lounasmaa's Second Generation Racemic Synthesis of Hirsutine (1998)

In 1998 Lounasmaa published a second generation synthesis of hirsutine, this time utilizing chemistry developed for their approach to geissoschizine and dihydrocorynantheol that employed a stereoselective Claisen rearrangement as a key step.[17] The synthesis commenced with the four-step preparation of the diastereomeric allylic alcohols **1.53** in 24% overall yield from tryptophyl bromide (**1.12**). This represented a slight improvement over Ziegler and Sweeney's approach to the same intermediate (five steps, 14% overall yield), which was used in their synthesis of

dihydrocorynantheol (*vide infra*).[18] After introducing a substituted vinyl group via 1,4-addition of **1.53** to methyl propiolate, the key Claisen rearrangement followed to deliver **1.55** and **1.56**, in a combined yield of 32% and a 5:4 ratio. Because of difficulties with separation, this mixture was treated with Boc_2O, after which the stereoisomers were easily separated to afford the pure stereoisomer **1.57** in 40% yield. At this point, all that remained was the conversion of **1.57** to **1.58** followed by hydrogenation of the ethylidine group to complete the synthesis of **1.5**. Unfortunately, virtually no diastereoselectivity was achieved in the latter transformation.

The strength of Lounasmaa's synthesis of hirsutine (**1.5**) was the key Claisen rearrangement, which allowed for the rapid installation the C15 appendage. However, while the synthesis was only nine steps, the low yield of the key step coupled with the need for three separations of almost equimolar mixtures of diastereomers makes this approach somewhat less efficient then several of the previous syntheses.

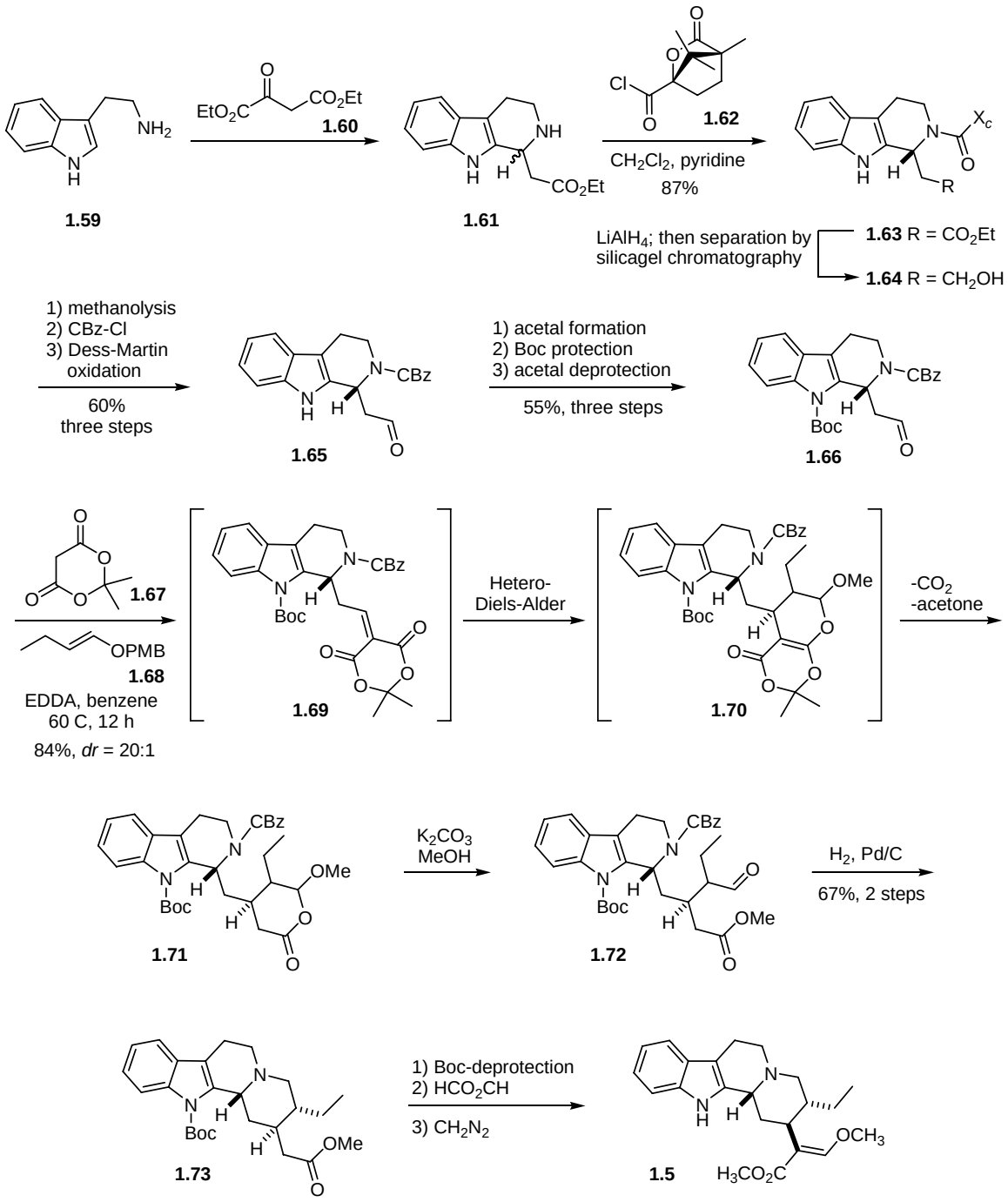
Scheme 1.8


Br
1.12
1.16
95%
Br⁻
1.17
N2S2O4, H2O
MeOH
45%
1.51
maleic acid,
Pd/C,H2O;
then NaClO4
60%
ClO4⁻
Boc
1.52
NaBH4
H2O, MeOH;
93%, dr = 1:1
1.53
H3CO
N-methylmorpholine
1,4 Dioxane
92%
H3CO2C
1.54
toluene, reflux
32%, dr = 5:4
1.55 H3CO2C
OH
1.56 H3CO2C
OH
Boc2O, DMAP
CH2Cl2
40%
1.57 H3CO2C
OBoc
HC(OCH3)3
TsOH, MeOH
25%
OCH3
1.58
H3CO2C
H2 / PtO2
MeOH
72%, dr = 1:1
1.5
OCH3
H3CO2C

1.2.10 Tietze's Enantioselective Total Synthesis (1999)

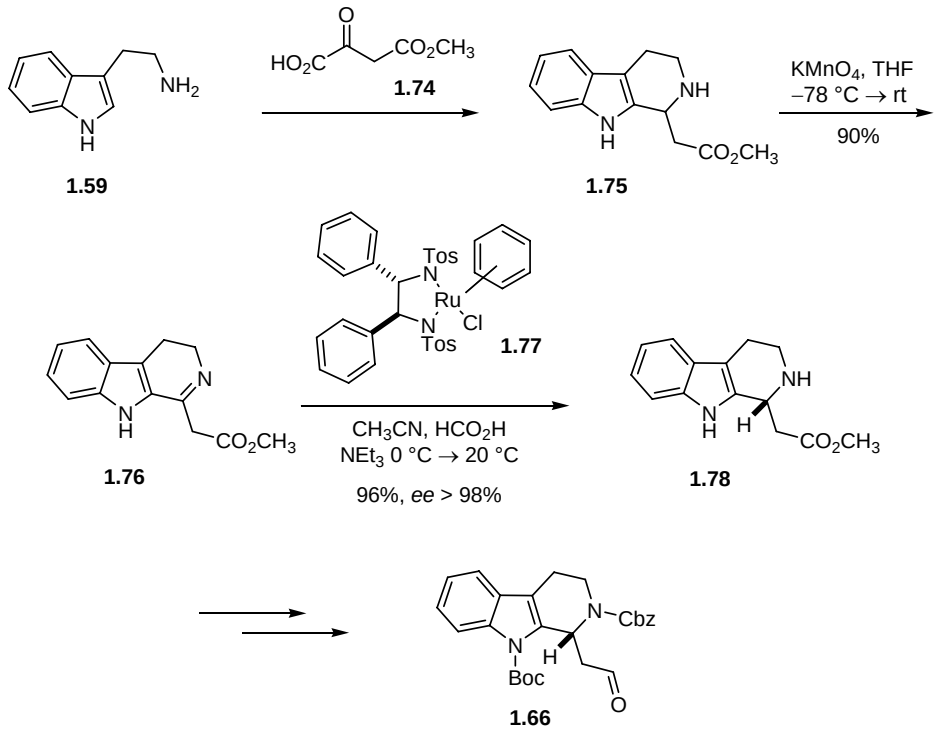
Perhaps the most interesting contribution came from the Tietze laboratory,[19] and their synthesis represents the most concise enantioselective approach to hirsutine to date. Additionally, the Tietze synthesis also constitutes a biomimetic approach involving a highly regio- and diastereoselective tandem reaction as a key step to rapidly construct the fully functionalized D-ring. As depicted in Scheme 1.9, sonication of a solution of aldehyde **1.66**, Meldrum's acid **1.65**, enolether **1.68**, and a catalytic amount of ethylenediamine diacetate (EDDA) in benzene for 12 hours effected an intermolecular Knoevenagel condensation to afford the 1-oxa-1,3-butadiene **1.69**. This highly reactive intermediate immediately underwent a hetero Diels-Alder reaction with enol ether **1.68** present in the reaction mixture to furnish cycloadduct **1.70**, which in turn suffered *in situ* thermolysis involving the loss of acetone and carbon dioxide to provide cycloadduct **1.71** in 84% yield and in a 20:1 diastereomeric ratio. Solvolysis of the crude **1.71** afforded aldehyde **1.72**, which upon hydrogenolysis of the Cbz group underwent cyclization to form the tetracyclic indoloquinolizidine intermediate **1.73**. From this point, only three transformations remained to complete the synthesis of **1.5**; deprotection of the Boc-group, condensation with methyl formate and methylation with diazomethane.

Scheme 1.9


1.59
1.60
1.61
1.62
CH2Cl2, pyridine
87%
LiAlH4; then separation by silicagel chromatography
1.63 R = CO2Et
1.64 R = CH2OH
1) methanolysis
2) CBz-Cl
3) Dess-Martin oxidation
60%
three steps
1.65
1) acetal formation
2) Boc protection
3) acetal deprotection
55%, three steps
1.66
1.67
1.68
OPMB
EDDA, benzene
60 C, 12 h
84%, dr = 20:1
1.69
Hetero-Diels-Alder
1.70
-CO2
-acetone
1.71
K2CO3
MeOH
1.72
H2, Pd/C
67%, 2 steps
1.73
1) Boc-deprotection
2) HCO2CH
3) CH2N2
1.5

While the elegant domino-sequence was an efficient way to construct the indoloquinolizidine ring system, the approach required a total of fifteen steps to complete the synthesis of **1.5**. An obvious shortcoming was the fairly lengthy sequence that was required to prepare the enantiopure aldehyde **1.66**, which involved chromatographic separation of a mixture (1:1) of diastereomeric amides **1.63** derived from camphanic acid. This issue was addressed in a later publication, in which an enantioselective approach to tetrahydro-β-carbolines and tetrahydroisoquinolines was developd.[20] As outlined in Scheme 1.10, racemic 1,2,3,4-tetrahydro-β-carbolines such as **1.75** were obtained via a Pictet-Spengler reaction of tryptamine (**1.59**) with keto acid **1.74**. This intermediate could then be oxidized with solid $KMnO_4$ to provide imine **1.76**. An asymmetric ruthenium catalyzed transfer hydrogenation using **1.77** then provided the requisite carboline derivative **1.78** in excellent yield (96%) and enantiomeric excess (>98%). Further functional group transformation finally yielded the requisite aldehyde **1.66** *en route* to hirsutine. The improved route to **1.66** reduced the length of the synthesis of hirsutine with a few steps.

Scheme 1.10


NH2
N
H
1.59
O
HO2C
CO2CH3
1.74
NH
N
H
CO2CH3
1.75
KMnO4, THF
−78 °C → rt
90%
Tos
N
Ru
Cl
N
Tos
1.77
N
N
H
CO2CH3
1.76
CH3CN, HCO2H
NEt3 0 °C → 20 °C
96%, ee > 98%
NH
N
H
H
CO2CH3
1.78
N
Cbz
N
H
Boc
O
1.66

1.3 RHYNCHOPHYLLINE AND ISO-RHYNCHOPHYLLINE

1.3.1 Background

Rhynchophylline (**1.7**) and its C(7) epimer iso-rhynchophylline (**1.8**) were first isolated by Kondo and co-workers in the early 1900's from the aerial parts of *Uncaria Rhynchophylla* (Rubiaceae).[21] There are approximately fifty species of this vine-like plant distributed throughout the tropical regions around the world, and many have found use in traditional medicine. For example, various species of *Uncaria* have been employed in Malaysian traditional medicine for the treatment of cardiovascular disorders such as hypertension, and **1.7** and its **1.8** are believed to be the active principles. The investigation into the biological activity of **1.7** and **1.8** has continued until present time, and these alkaloids were recently found to protect against glutamate-induced neuronal death in cultured cerebellar granule cells.[22]

An *interesting* synthetic challenge associated with these alkaloids is the C(7) spirocenter, which is known to be configurationally labile. In fact, rhynchophylline (**1.7**) and *iso*-rhynchophylline (**1.8**) are known to equilibrate upon standing via a retro-Mannich/Mannich pathway. This is an important consideration when designing a synthesis of **1.7** and **1.8** since the early introduction of the oxindole function likely will result in epimerization of the C(7) spirocenter.

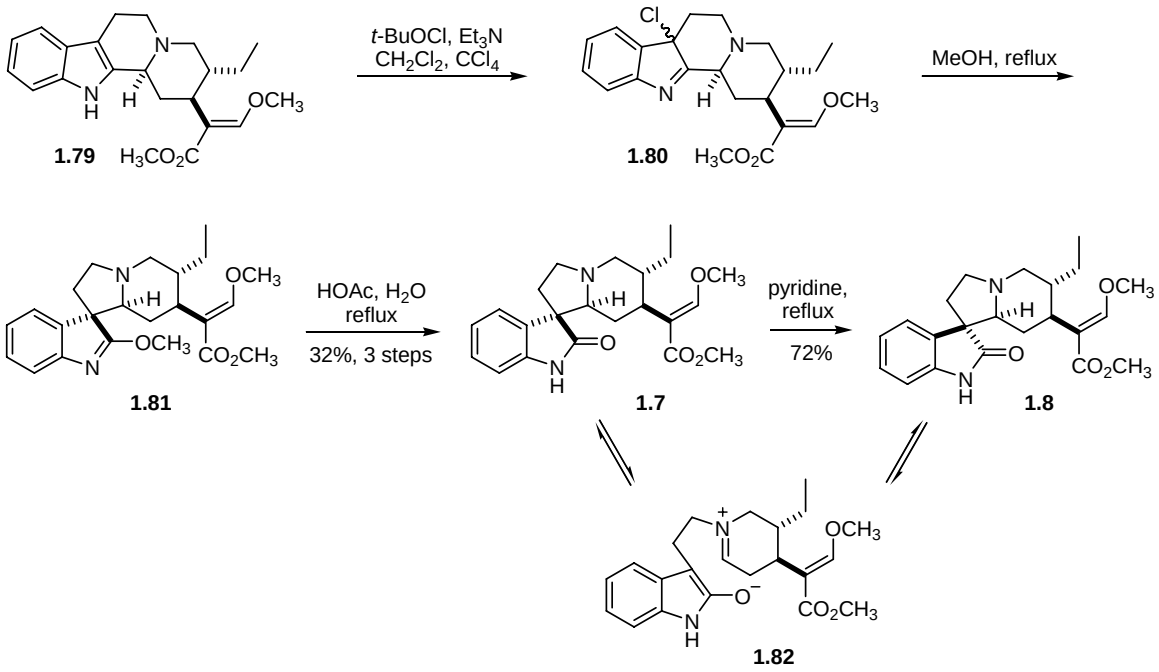
1.3.2 Finch and Taylor's Partial Syntheses of Rhynchophylline and Iso-rhynchophylline (1962)

Aside from a one-step conversion of corynoxeine to rhynchophylline in 1952,[23] the first partial synthesis of rhynchophylline was reported by Finch and Taylor in 1962.[7]

These workers examined the application of a biomimetic oxidative rearrangement to convert indole alkaloids to their corresponding oxindole counterparts. As depicted in Scheme 1.11, dihydrocorynantheine (**1.79**) was treated with *t*-butyl hypochlorite to chlorinate the C-3 position of the indole. The resultant chloroindole species **1.80** was refluxed in methanol to effect the conversion of **1.80** to imido ether **1.81**. Finally, **1.81** was refluxed in 10% acetic acid, which hydrolyzed the imido ether to the target oxindole **1.7** which could be isolated in 32% yield over the three steps.

Oxindole alkaloids are not configurationally stable at C(7) but undergo epimerization via a retro-Mannich/Mannich pathway as indicated in Scheme 1.11. The energy difference between the two epimers is very small as many oxindole natural products exist in nearly a one to one ratio. Interestingly, this equilibrium composition is slightly different in acidic and basic media with rhynchophylline being the predominant isomer in acidic solutions where as isorhynchophylline predominates under basic conditions. Finch and Taylor took advantage of this phenomenon by refluxing synthetic rhynchophylline (**1.7**) in pyridine overnight to convert it to isorhynchophylline (**1.8**), which could be isolated in 72% yield.

Scheme 1.11



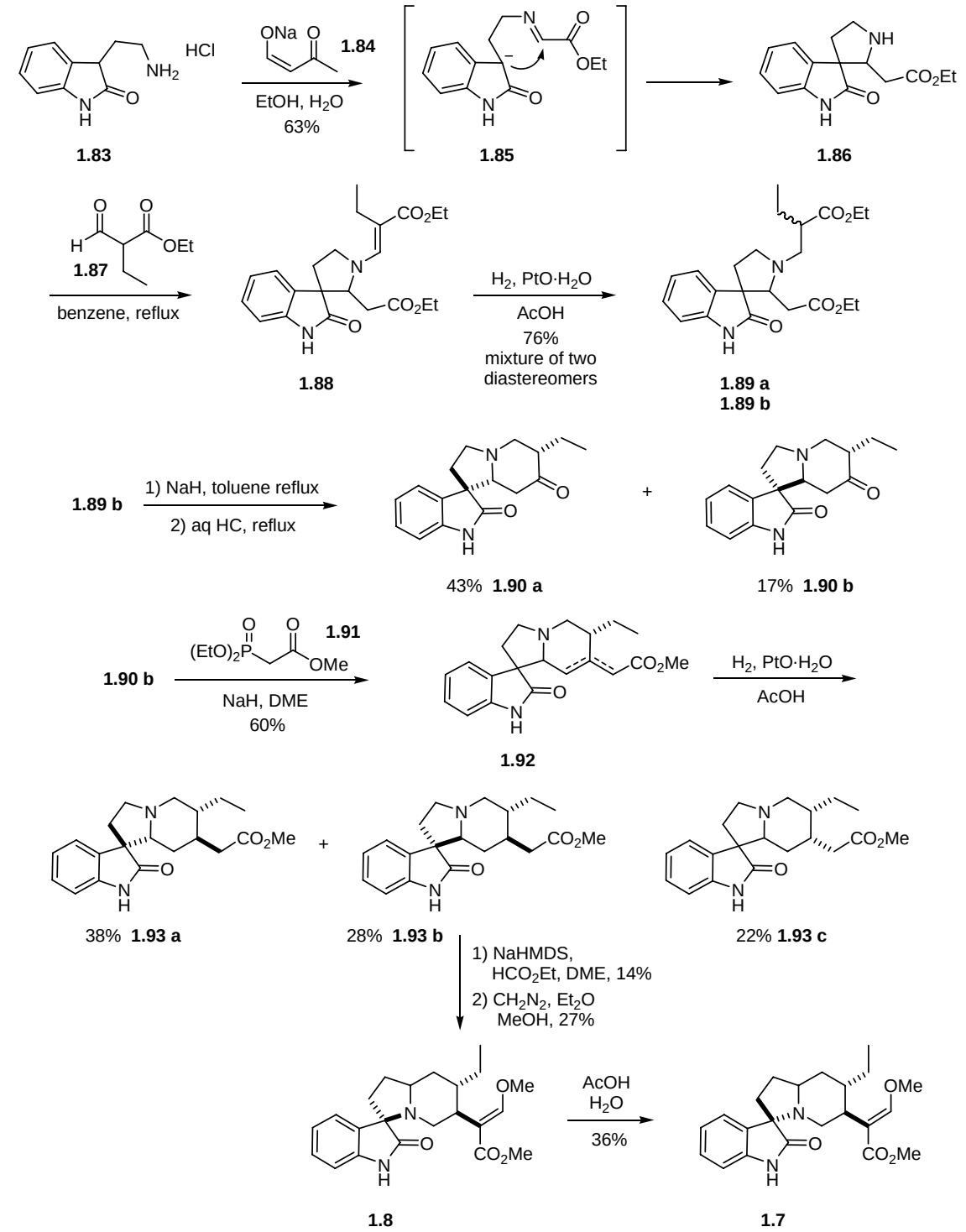
The studies on the oxidative rearrangements of indoles to oxindoles by Finch and Taylor, Seaton and Nair,[24] Acklin[25] as well as Martin,[26] have been of great importance in the area of oxindole alkaloid synthesis. To this day they continue to inspire the development of new, innovative methods for the construction of oxindoles as will be discussed in detail in chapters 3 and 4.

1.3.3 Ban's Racemic Total Syntheses of Rhynchophylline (1974)

The synthesis of **1.8** by Ban and co-workers[27] commenced with the condensation of 2-hydroxytryptamine hydrochloride (**1.83**) with ethyl sodium formyl acetate (**1.84**) to furnish **1.86** via the intermediacy of **1.85**. These reaction conditions were carefully optimized to avoid hydrolysis/decarboxylation of the ethyl ester. The resultant secondary amine **1.86** was then condensed with ethyl α-formyl butyrate (**1.87**) to give **1.88**, which in

turn was hydrogenated to furnish a mixture of diastereomers **1.89a** and **1.89b**. The lack of diastereoselectivity could be explained by epimerization of the spirocycle via a retro-Mannich/Mannich pathway during the acidic reaction conditions. After chromatographic separation of diastereomers, a diastereomerically pure sample **1.89b** was subjected to Diekmann condensation followed by acid catalyzed hydrolysis/decarboxylation to afford a mixture of the C(7) epimers **1.90a** and **1.90b**. The reaction could also be carried out starting with the other isomer **1.89a**. Following chromatographic separation of the diastereomers, **1.90b** was subjected to a Horner-Wadsworth-Emmons reaction with phosphonate **1.91** to give **1.92** as an unidentified mixture of olefin regio- and geometrical isomers. The mixture was hydrogenated using Adams' catalyst in acetic acid to afford the three saturated esters **1.93a, 1.93b**, **1.93c** in 38%, 28%, 22% yield respectively. This represented an improvement over earlier reaction conditions using palladium on carbon in ethanol which gave the three isomers in 6%, 26% and 37% yield. The stereochemistry of **1.93c** was not fully elucidated but the isomer was presumed to have the C(15)-C(20) *cis*-configuration. With the complete tetracyclic framework in hand, only three steps remained to complete the synthesis. Even though one could envision either isomer **1.93a** or **1.93b** as being carried forward, only **1.93b** was elaborated to the final targets. Thus, condensation with ethyl formate followed by methylation with diazomethane furnished iso-rynchophylline (**1.8**). The natural product was then be epimerized under acidic conditions to finally yield rhynchophylline (**1.7**) in 10 steps from 2-hydroxytryptamine (**1.83**).

Scheme 1.12


HCl
NH2
ONa O
1.84
EtOH, H2O
63%
1.83
1.85
1.86
1.87
benzene, reflux
1.88
H2, PtO·H2O
AcOH
76%
mixture of two
diastereomers
1.89 a
1.89 b
1.89 b
1) NaH, toluene reflux
2) aq HC, reflux
43% 1.90 a
17% 1.90 b
1.91
1.90 b
NaH, DME
60%
1.92
H2, PtO·H2O
AcOH
38% 1.93 a
28% 1.93 b
22% 1.93 c
1) NaHMDS,
HCO2Et, DME, 14%
2) CH2N2, Et2O
MeOH, 27%
AcOH
H2O
36%
1.8
1.7

1.4 DIHYDROCORYNANTHEOL

1.4.1 Background

The archetypal corynanthe alkaloid dihydrocorynantheol (**1.6**) was first isolated in 1962 by Djerassi and co-workers.[28] It was obtained from the bark of *Aspidosperma marcgravianum* Woodson (Apocynaceae), and it has been shown to possess antimicrobial activity against Gram-positive bacteria.[29] While closely related to hirsutine (**1.5**), dihydrocorynantheol (**1.6**) possesses the more thermodynamically stable "normal" configuration (C(3)-H α, C(15)-H α, C(20)-H β).

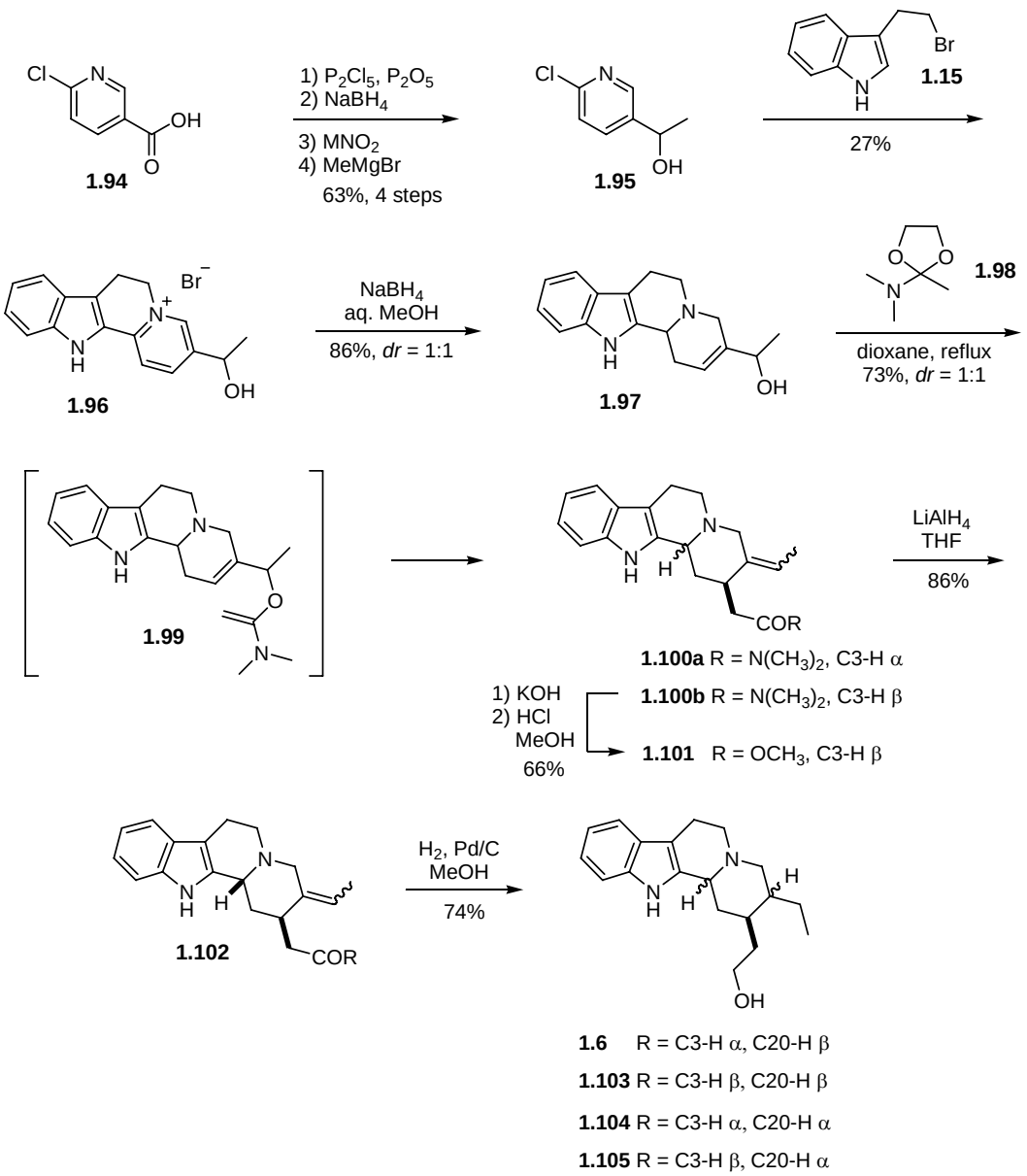
Dihydrocorynantheol has been a popular target for showcasing new methodologies and synthetic strategies, and a substantial amount of work has been recorded in the literature. Several of the early accounts were semi-syntheses using other alkaloids as starting material. Thus, dihydrocorynantheol has been prepared from dihydrocorynantheine,[30] geissoschizol,[31] quinine,[32] ajmalicine[33] and guettardine.[34] The first total syntheses of **1.6**, appeared as early as 1969 and was published by Ziegler and Sweeny (*vide infra*).[18]

1.4.2 Zieglers's Synthesis of Dihydrocorynantheol and 3-*epi*-Dihydrocorynantheol (1969)

The key step in the synthesis by Ziegler and Sweeny[18] was a reaction developed by Eschenmoser,[35] in which allylic alcohol **1.97** was condensed with dimethylacetamide dimethylacetal (**1.98**) resulting in an intermediate **1.99** that was poised to undergo a Claisen rearrangement (Scheme 1.13). The synthesis commenced with the elaboration of 6-chloronicotinic acid (**1.94**) to furnished secondary alcohol **1.95**, which was alkylated with tryptophyl bromide to afford **1.96** in modest yield (27%). Reduction of **1.96** with

sodium borohydride then delivered the key intermediate **1.97** as mixture (1:1) of diastereomers. Upon refluxing this mixture in dioxane in the presence of dimethylacetamide dimethylacetal (**1.98**), amides **1.100a and 1.100b** were formed in 73% yield as a mixture of 4 different isomers due to the formation of diastereomers and olefin *E*/*Z* isomers. Amides **1.100a** and **1.100b** could be separated by prep-TLC, although both were isolated as a mixture of *E*/*Z* isomers. Amide **1.100b** was then subjected to hydrolysis, Fisher esterification, and $LiAlH_4$ reduction to deliver **1.102**, again as mixture of *E*/*Z* isomers. Finally, hydrogenation of the olefin afforded **1.103** the major product and dihydrocorynantheol (**1.6**) as the minor constituent.[36] Interestingly, **1.102** resulted from epimerization of the C(3) stereocenter during the hydrogenation conditions.

Scheme 1.13



This eleven step synthesis represents an excellent example of the challenges involved in designing an efficient approach to the corynanthe alkaloids, namely controlling the stereochemistry of the C(3), C(15), and C(20) stereocenters around the D-ring. While it incorporates an interesting tactic for the introduction of the C(15)

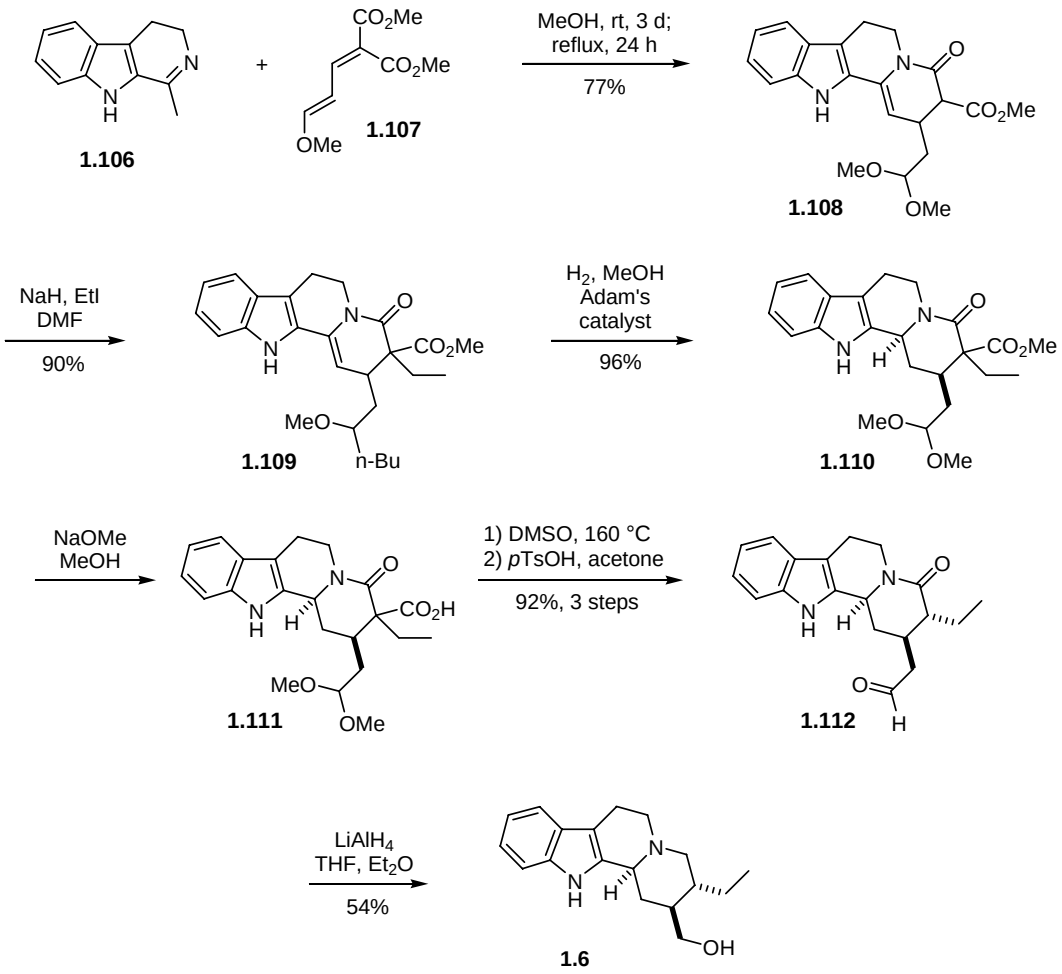
substituent, Ziegler's approach fell short with regard to controlling stereochemistry, and this challenge has continued to inspire chemist up to present time.

1.4.3 Kametani's Total Synthesis of Dihydrocorynantheol (1980)

In contrast to Zieglers's approach, Kametani offered an elegant solution to the challenge of controlling the D-ring stereochemistry.[37] Kametani's synthesis utilized an enamine annelation of 3,4-dihydro-1-methyl-8-carboline (**1.106**), which is available in two steps from tryptamine, with 3-methoxy-allylidinemalonate (**1.107**) to afford **1.108** in 77% yield as a single stereoisomer. Following introduction of the ethyl substituent via alkylation, the olefin of **1.109** was reduced by hydrogenation using Adams's catalyst to afford **1.110** in 96% yield as a single stereoisomer. The hydrogenation was presumed to occur from the sterically more accessible face to give **1.110** exclusively. Interestingly, two stereoisomers were formed in this reaction if palladium on carbon was used as the catalyst rather than Adam's catalyst (PtO_2).

Following saponification of the methyl ester, the β-keto acid **1.111** underwent decarboxylation upon heating to 160 °C in DMSO. The acetal was partially hydrolyzed to the aldehyde during the decarboxylation reaction, and exposure of the resultant mixture to pTsOH cleanly afforded **1.112** in 92% yield from **1.111**. Finally, the aldehyde and the lactam were reduced by the action of $LiAlH_4$ to afford the natural product **1.6** in 54% yield.

Scheme 1.14

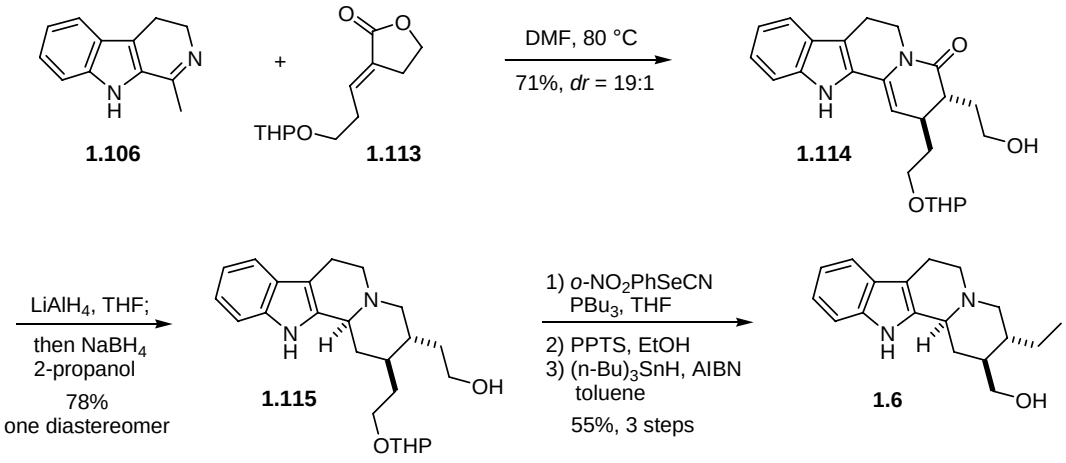


The level of stereocontrol in this synthesis is remarkable. While the stereochemistry of **1.108**, **1.109** and **1.110** was not fully elucidated, each was formed as a single stereoisomer. The synthesis consists of nine steps from tryptamine in its longest linear sequence. However, while it is a simple and elegant synthesis, Kametani's synthesis, unlike other approaches to this molecule, does not readily lend itself to the enantioselective preparation of **1.6**.

1.4.4 Danieli and Palmisano's Total Synthesis of Dihydrocorynantheol (1981)

The synthesis of **1.6** by Danieli and Palmisano was very similar to that of Kametani in that it utilized the 1,4-addition of **1.106** to an enoate.[38] In this case lactone **1.113** was used, which was available in three steps from 1,3-propanediol. Following the successful 1,4-addition, a lactone-lactam rearrangement spontaneously ensued to deliver **1.114** in 71% yield and 19:1 diastereoselectivity. Danieli then devised an interesting solution to the problem of diastereoselectively and reduced the enamine of **1.114** to control the C(3) stereochemistry. Following reduction of the lactam with $LiAlH_4$, a solution of $NaBH_4$ in 2-propanol was added. This resulted in the protonation of the enamine function to give an iminium ion, which was reduced to furnish **1.115** with complete stereoselectivity. Deprotection of the THP group followed by reductive removal of the primary hydroxyl group via the selenide then afforded the target **1.6**.

Scheme 1.15



The synthesis described above was fairly concise affording **1.6** in eight steps in its longest linear sequence (ten steps total) and with a high degree of stereoselectivity.

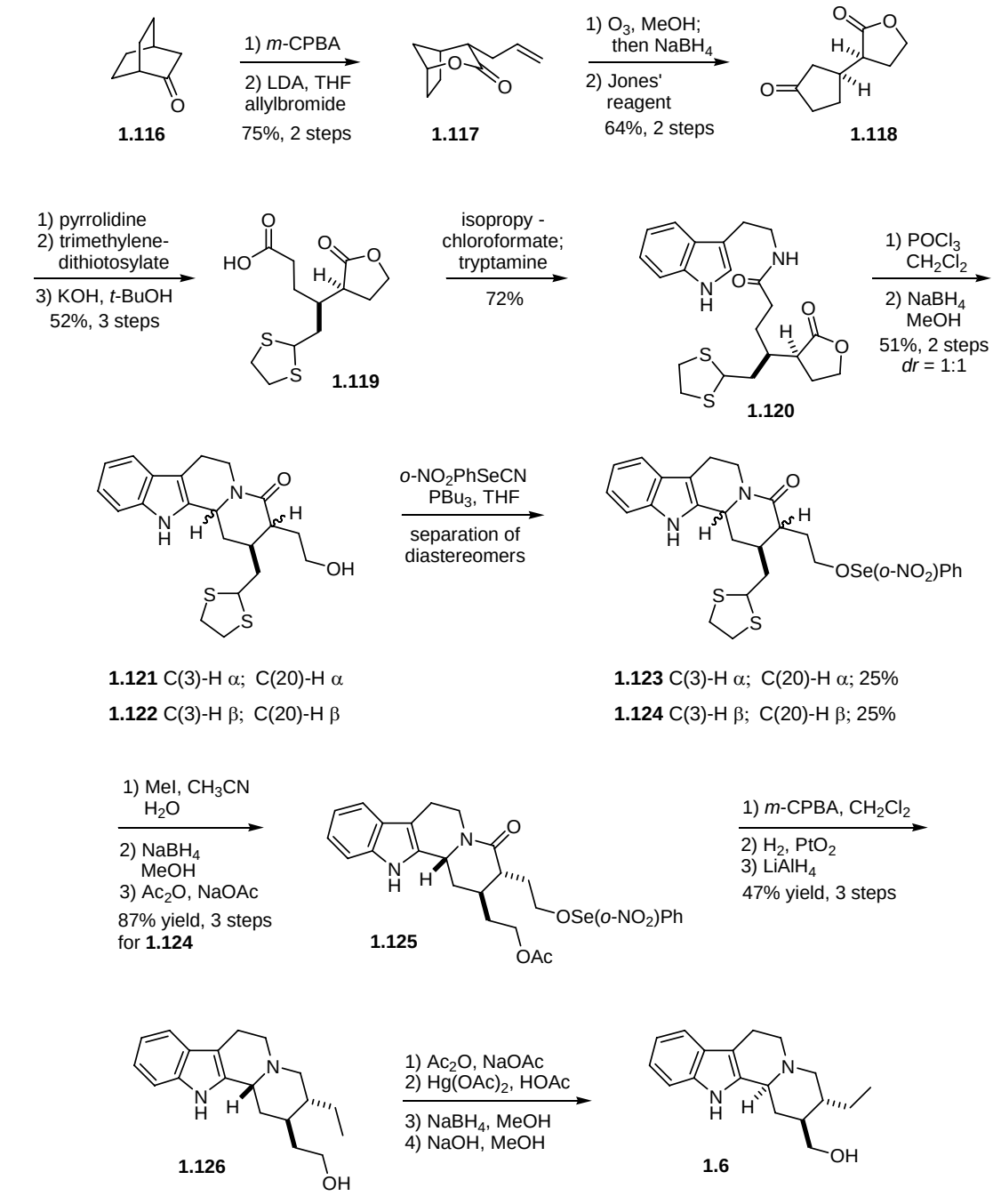
However, like Kametani's approach, there was no apparent way to render the strategy enantioselective.

1.4.5 Takano's Total Synthesis of Dihydrocorynantheol (1981)

Takano and co-workers developed an approach that allowed access to alkaloids of all four possible stereochemical configurations; normal, allo, pseudo, and epi-allo, through epimerizations and separation of diastereomers at various stages of the synthesis.[39] Two routes to dihydrocorynantheol were actually developed; however, the one presented in Scheme 1.16 was the most efficient requiring only one separation of diastereomers.

Carboxylic acid **1.119**, which was prepared in seven steps from (±)-norcamphor (**1.116**), was coupled with tryptamine via a mixed anhydride to afford **1.120** in 72% yield. Bishler-Napieralski reaction of **1.120** followed by $NaBH_4$ reduction of the resultant iminium hydrochloride salt proceeded with spontaneous lactam formation to give **1.121** and **1.122** in 51 % yield as an equimolar mixture of diastereomers. This mixture could be separated following conversion of **1.121** and **1.122** to the corresponding selenides **1.123** and **1.124**. Elaboration of **1.124** to dihydrocorynantheol (**1.6**) was then accomplished in ten relatively straightforward steps, with the last four transformation being devoted to the epimerization of the C(3)-proton. By choosing norcamphor (**1.116**) as the starting material, Takano ensured that the synthesis would readily lend itself to the enantioselective preparation of **1.6**. However, the synthesis was relatively lengthy requiring a total of 21 steps to afford the natural product.

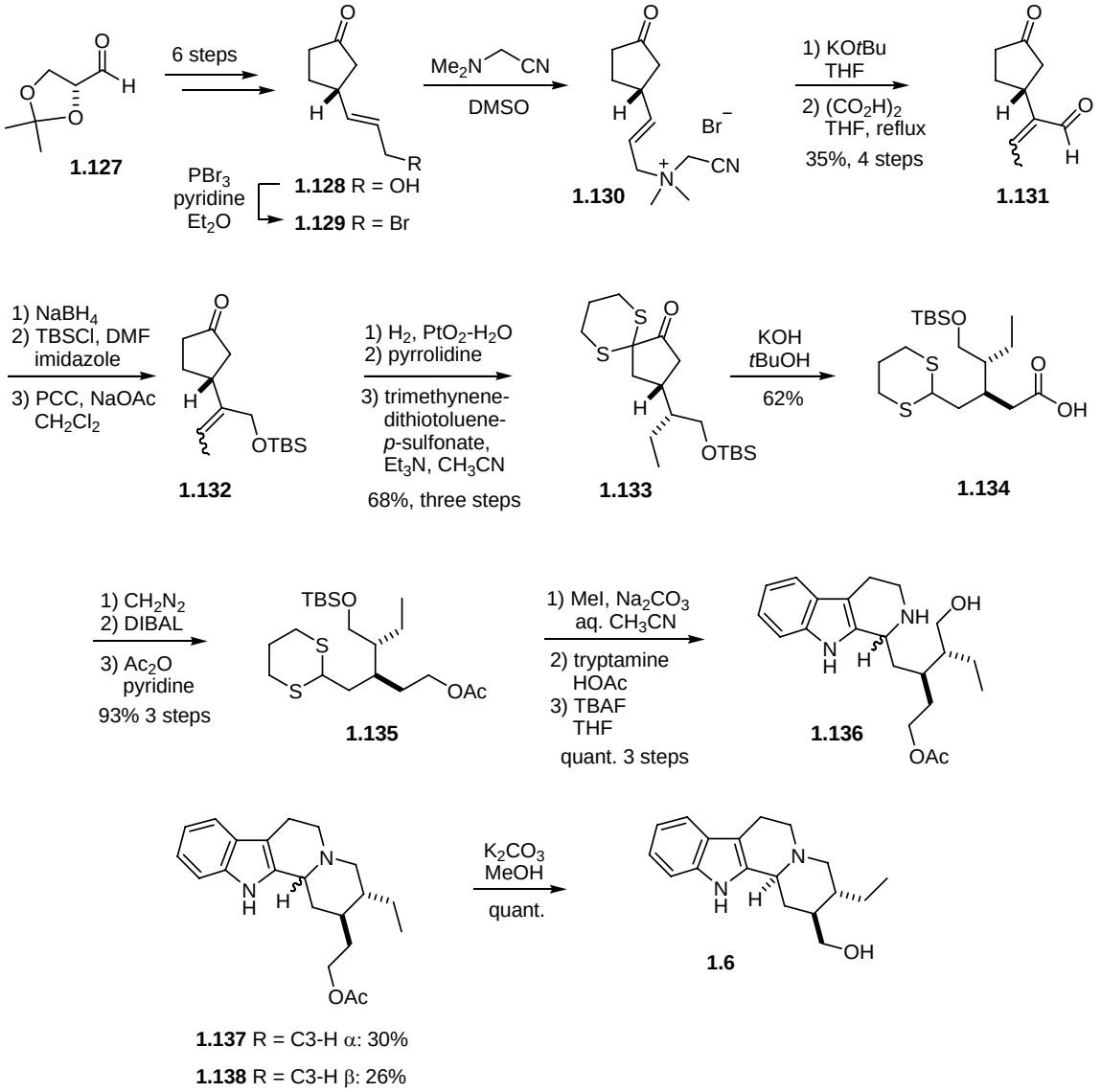
Scheme 1.16


1) m-CPBA
2) LDA, THF
allylbromide
75%, 2 steps
1) O3, MeOH;
then NaBH4
2) Jones'
reagent
64%, 2 steps
1.116
1.117
1.118
1) pyrrolidine
2) trimethylene-
dithiotosylate
3) KOH, t-BuOH
52%, 3 steps
isopropy -
chloroformate;
tryptamine
72%
1) POCl3
CH2Cl2
2) NaBH4
MeOH
51%, 2 steps
dr = 1:1
1.119
1.120
o-NO2PhSeCN
PBu3, THF
separation of
diastereomers
1.121 C(3)-H α; C(20)-H α
1.122 C(3)-H β; C(20)-H β
1.123 C(3)-H α; C(20)-H α; 25%
1.124 C(3)-H β; C(20)-H β; 25%
1) MeI, CH3CN
H2O
2) NaBH4
MeOH
3) Ac2O, NaOAc
87% yield, 3 steps
for 1.124
1.125
1) m-CPBA, CH2Cl2
2) H2, PtO2
3) LiAlH4
47% yield, 3 steps
1) Ac2O, NaOAc
2) Hg(OAc)2, HOAc
3) NaBH4, MeOH
4) NaOH, MeOH
1.126
1.6

1.4.6 Suzuki and Kametani's Enantioselective Synthesis of (-)-Dihydrocorynantheol (1985)

The first enantioselective synthesis of **1.6** was reported by Suzuki and Kametani in 1985.[40] The chirality was derived from (*R*)-1,2-isopropylidineglyceraldehyde (**1.127**), which was elaborated to cyclopentenone **1.128** via a seven-step sequence involving chirality transfer using an orthoester Claisen rearrangement. The chiral synthon **1.128** was further elaborated in nine steps using a 2,3-sigmatropic rearrangement and a stereoselective hydrogenation as key steps to provide thioketal carboxylic acid **1.134**, bearing the two adjacent stereocenters that would eventually become the C(15) and C(20) carbons of the D-ring. Following conversion of the carboxylic acid function to acetate **1.135**, the dithiane was deprotected to reveal an aldehyde that underwent a Pictet-Spengler reaction with tryptamine. After removal of the silyl protecting group, **1.136** could be obtained in almost quantitative yield over the three steps. Unfortunately, there did not seem to be any significant stereocontrol in the Picted-Spengler reaction. While the two diastereomers were inseparable at this stage, following ring-closure via mesylation and intramolecular alkylation, the two indoloquinolizidines **1.137** and **1.138** were isolated in 30% and 26% respectively. One should note that it was possible to convert **1.138** to **1.137** via a two step sequence by the dehydrogenation with $Hg(OAc)_2$ to give an iminium ion which was then reduced with $NaBH_4$. Finally, hydrolysis of the acetate of **1.137** afforded (-)-dihydrocorynantheol (**1.6**) in quantitative yield.

Scheme 1.17

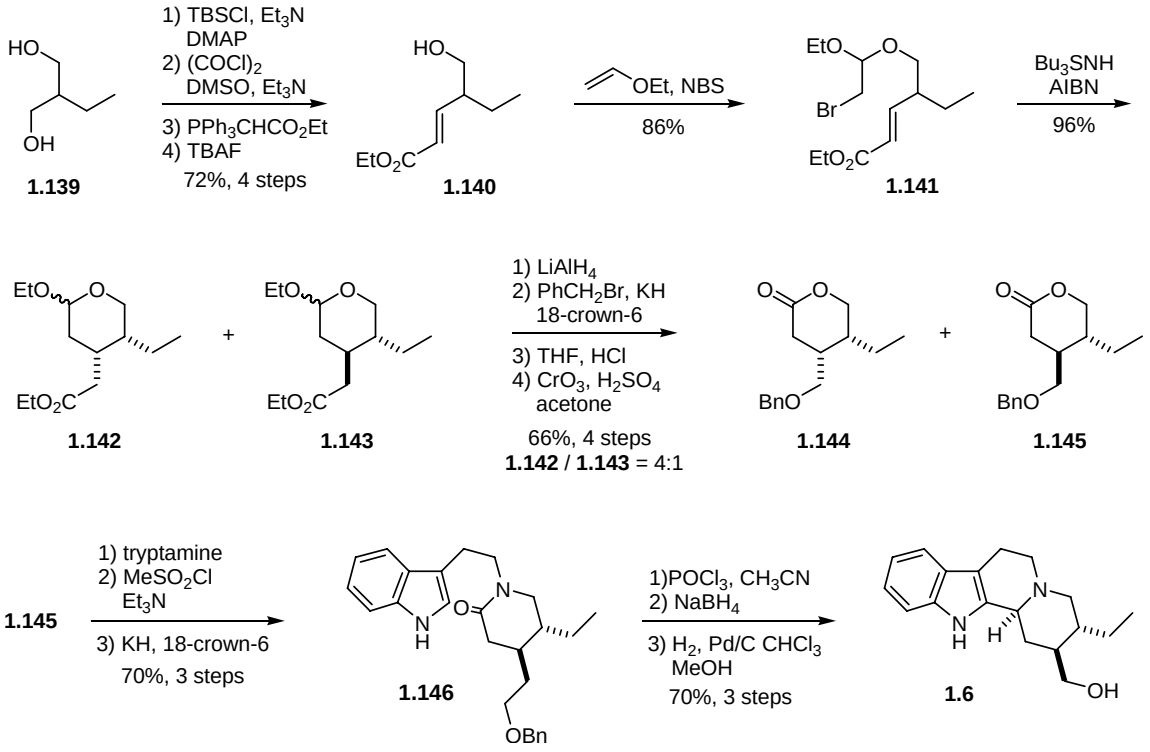


While these efforts did result in the first enantioselective synthesis of dihydrocorynantheol, the synthesis was exceedingly lengthy, requiring a total of 23 steps from (*R*)-1,2-isopropylidineglyceraldehyde (**1.127**). Furthermore, there was virtually no stereocontrol in the Pictet-Spengler reaction resulting in a roughly mixture (1:1) of C(3) epimers, which had to be separated by chromatography.

1.4.7 Fukumoto's Total Synthesis of Dihydrocorynantheol (1987)

In his synthesis of dihydrocorynantheol, Fukumoto employed a radical cyclization as a key step to construct the D-ring and to control the relative stereochemistry of the C(15) and C(20) stereocenters.[41] When enoate **1.141**, which was prepared in five steps from 2-ethylpropane-1,3-diol,[42] was treated with tributyltinhydride in the presence of AIBN, the corresponding tetrahydropyran derivatives **1.142** and **1.143** were formed in 94% yield as a mixture of all four possible diastereomers (Scheme 1.18). This reaction could also be carried out using the corresponding α-bromo ester of **1.141** to give a single diastereomer, albeit in only 35% yield. The mixture of **1.142** and **1.143**, which could not be separated at this stage, was further elaborated through four steps to give **1.144** and **1.145** in a 4:1 ratio, which could be separated by HPLC. The major isomer **1.144** was then condensed with tryptamine, which following mesylation of the resultant alcohol and exposure to KO*t*Bu, afforded the indole derivative **1.146** in 70% yield. Finally, Bischler-Napieralski reaction and stereoselective reduction completed the total synthesis of **1.6**.

Scheme 1.18



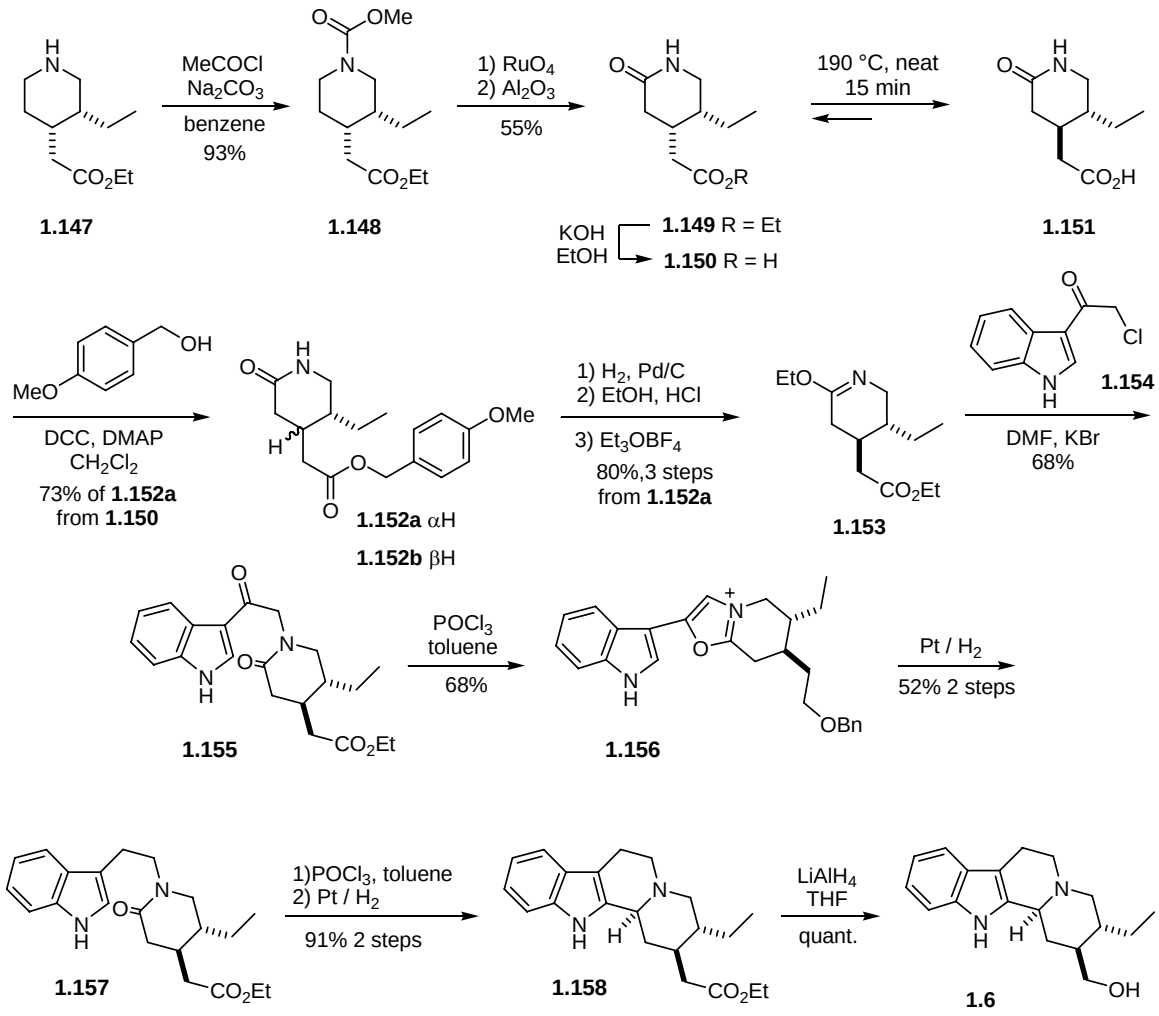
Fukumoto's approach, which was sixteen steps from **1.139**, featured an interesting strategy for controlling the stereochemistry around the D-ring. However, the need for carrying a mixture of four diastereomers through a four-step sequence coupled with the low level of diastereoselectivity in the radical cyclization (4:1) leaves room for further improvement.

1.4.8 Fuji's Enantioselective Synthesis of (-)-Dihydrocorynantheol (1991)

Fuji and co-workers developed a gram-scale enantioselective synthesis of **1.6**. The synthesis started from piperidine **1.147**, which was available through degradation of (+)-cinchonine or through completely synthetic means. A major challenge in the synthesis was the equilibration of the 3,4-*cis* piperidine **1.150** to the 3,4-*trans* derivative **1.151**,

which gave a mixture (66:34) of unseparable diastereomers. Fuji found that the diastereomeric *p*-methoxybenzoate derivatives **1.152a** and **1.152b** could be readily separated by crystallization. Following removal of the protecting group of the unwanted diastereomer **1.152b**, this material was then resubmitted to the equilibration protocol resulting in a 73% combined yield of **1.152a** from **1.150** after two recycles. The synthesis could then be completed in nine steps in a relatively straightforward manner. The strength of Fuji's approach, which required 14 steps from **1.147**, was that it allowed for the preparation of **1.6** on gram scale. This was a significant improvement over the previous enantioselective synthesis, which only afforded **1.6** in milligram quantities.[40] On the other hand, the synthesis was quite lengthy when considering the number of steps required to prepare the starting material **1.147**. Additionally, only modest levels of stereoselectivity were obtained in the equilibration protocol resulting in the need to recycle the unwanted diastereomer twice through a three-step sequence in order to obtain a satisfactory yield of **1.152**.

Scheme 1.19

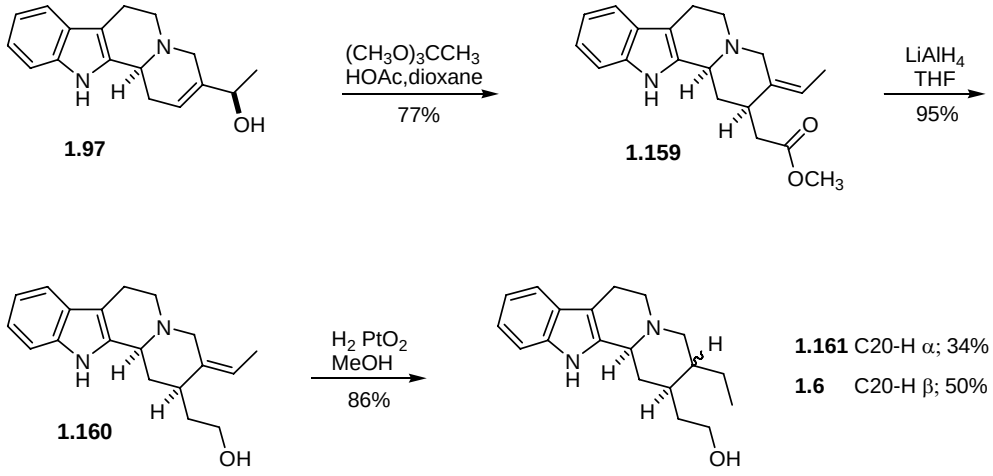


1.4.9 Lounasmaa's Synthesis of (-)-Dihydrocorynantheol (1991)

Louansmaa and co-workers decided to re-examine the approach described by Ziegler and Sweeny, in which a diastereomeric mixture of allylic alcohols served as precursors for a key Claisen rearrangement.[18] Lounasmaa reasoned that if diastereomerically pure allylic alcohol **1.97** was used in the Claisen rearrangement, one

would likely be able to attain high levels of diastereoselectivity. Using an improved route to the pure diastereomer **1.97** that involved separating diastereomers through successive fractional crystallization (*vide supra*),[15] they then attempted the direct conversion of **1.97** to **1.159** using trimethyl orthoacetate. While a diastereomeric ratio was not given, the reaction clearly exhibited some diastereoselectivity since the desired diastereomer was isolated cleanly in 77% yield. Following reduction of the ester to a primary alcohol **1.160**, only the hydrogenation of the exocyclic olefin remained to complete the synthesis. However, as was observed by Ziegler and Sweeny, this reaction proceeded with virtually no diastereoselectivity to deliver **1.6** in 50% yield following chromatographic separations of the two diastereomers. Lounasmaa's synthesis of hirsutine only required seven steps from tryptophyl bromide, and it is therefore the shortest synthesis of **1.6**. However, it was not diastereoselective and required two separations of virtually equimolar mixtures of diastereomers.

Scheme 1.20

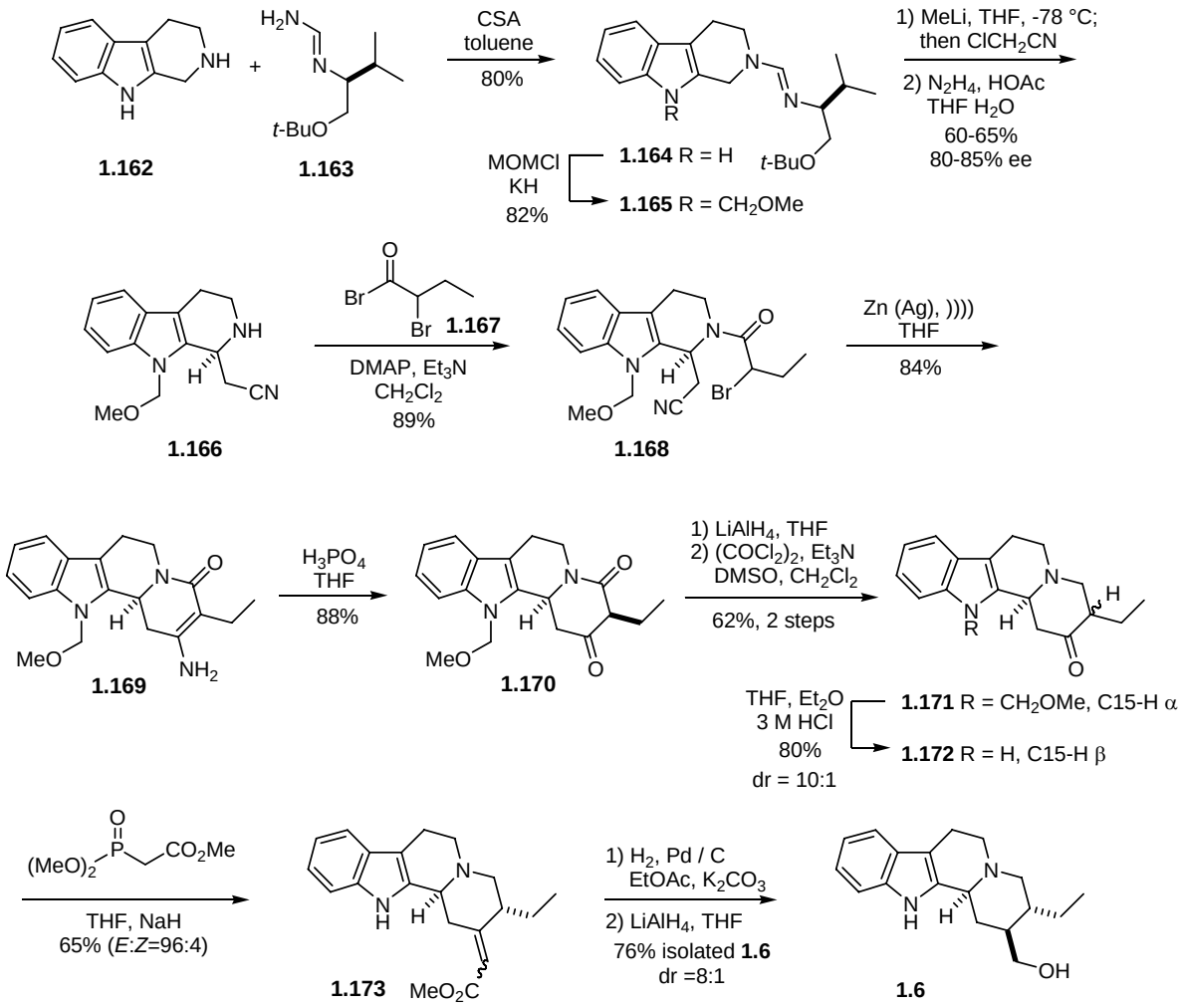


1.4.10 Meyers' Enantioselective Synthesis of (-)-Dihydrocorynantheol (1991)

Meyers' synthesis represents an elegant solution to the challenge of controlling both the relative and absolute stereochemistry.[43] His strategy involved directed lithiation of carboline derivative **1.165** bearing a chiral formamidine directing group. Using this tactic, cyanomethyl substituted carboline **1.166** was obtained in up to 65% yield and 85% ee (Scheme 1.21). Acylation of the resultant secondary amine **1.166** with 2-bromobutanoyl chloride (**1.167**) then set the stage for a rarely used Blaise reaction using zinc-silver couple and sonication to construct the D-ring and provide **1.169** in 84% yield. Interestingly, following additional functional group transformation to give **1.171**, it was discovered that the C(15) ethyl group cleanly underwent epimerization under the acidic MOM deprotection conditions to provide **1.172** in 84% yield and 10:1 diastereoselectivity. Ketone **1.172** was then subjected to a Horner-Wadsworth-Emmons olefination followed by diastereoselective hydrogenolysis and reduction of the ethyl ester to complete the total synthesis of **1.6**.

The control of relative stereochemistry was generally good through out the synthesis, but the approach required a total of 13 steps from commercially available carboline **1.62**. While this is somewhat lengthy, it is a considerable improvement over previous enantioselective syntheses of **1.6**. It is noteworthy that Meyers asymmetric approach to dihydrocorynantheol also could be used to prepare the closely related natural product corynantheidol, which differs from dihydrocorynantheol only in the stereochemistry of the C(20) ethyl substituent. Simply by delaying the deprotection of the MOM group until the last step of the synthesis, the epimerization of the C(20) ethyl group was avoided, thus providing corynantheidol through an analogous reaction sequence.[43]

Scheme 1.21



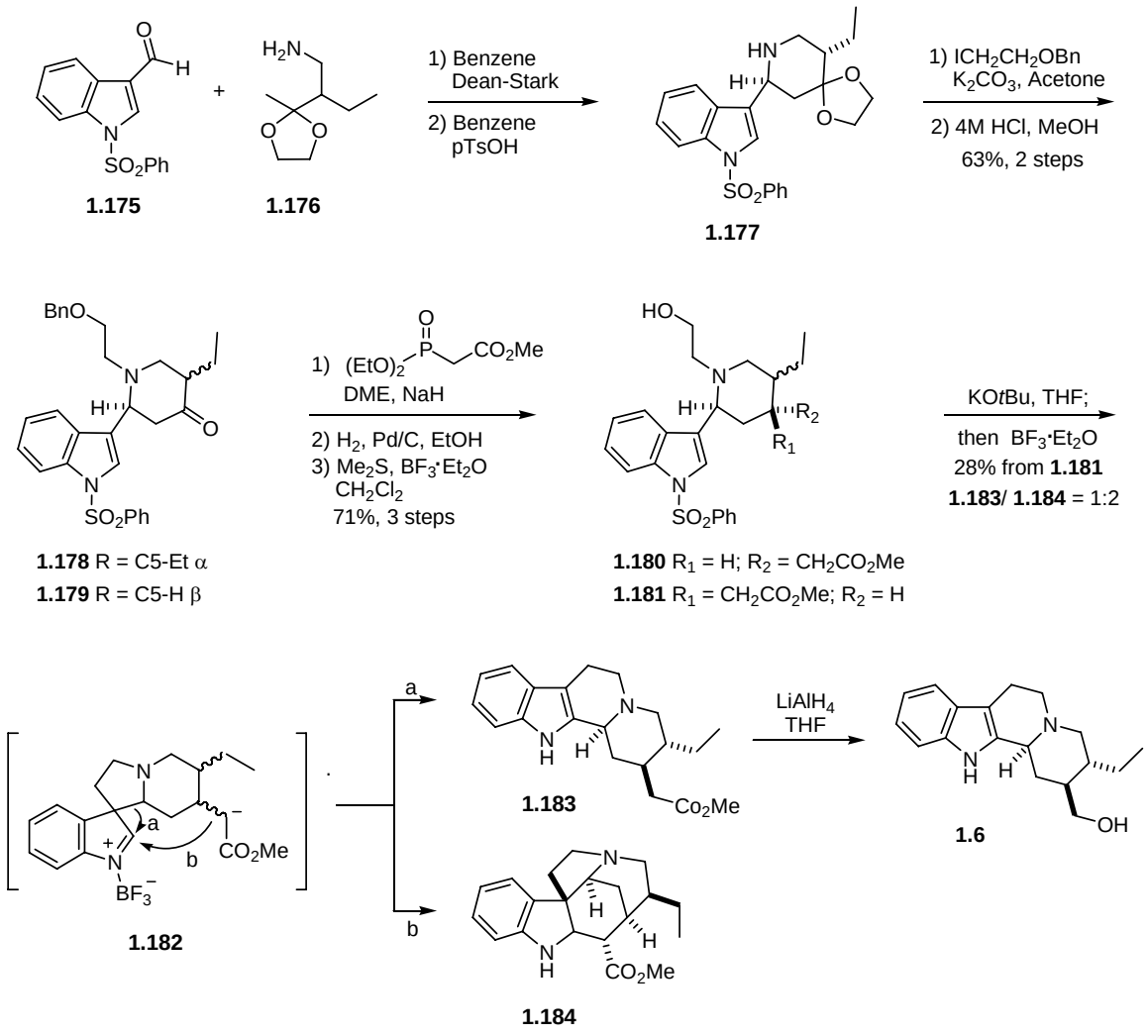
1.4.11 Rubiralta's Synthesis of Dihydrocorynantheol (1993)

Rubiralta and co-worker used a rather different approach to dihydrocorynantheol as compared with previous synthesis.[44] Rather than the classical ABD→ABCD approach, their strategy involved the formation of spiroindolenine **1.182** upon exposure of **1.181** to KOtBu. Lewis acid activation of the imine nitrogen of **1.182** resulted in the formation of

two new products. As shown in Scheme 1.22, path b involved the attack of the ester enolate onto the C(2) position of the indole delivering tetrahydroakummicine **1.184** with the characteristic carbon skeleton of the *Strychnos* alkaloids. Path a, on the other hand, involved a C(3)-C(2) bond migration to furnish **1.183**. The two products **1.183** and **1.184** were obtained in a combined yield of 28% in a 1:2 ratio, and with **1.183** in hand, the synthesis of dihydrocorynantheol (**1.6**) could be completed by the reduction of the ester to the primary alcohol (Scheme 1.22).

The synthesis of dihydrocorynantheol (**1.60**) was completed in nine steps from **1.175** and **1.176**, but the brevity of the sequence was offset by the low yield and poor selectivity of the key step. Moreover, the synthesis leading up to the substrates **1.181** was complicated by a lack of stereocontrol. For example, when the acetal function in piperidine **1.177** was hydrolyzed under acidic conditions, the C(5) stereocenter bearing the ethyl group was epimerized to a 2.5:1 ratio of *cis* to *trans* isomers. Likewise, the hydrogenation of the enoates resulting from the HWE olefination of **1.178** and **1.179** resulted in a complicated mixture of diastereomers that had to be separated prior to performing the key step.

Scheme 1.22

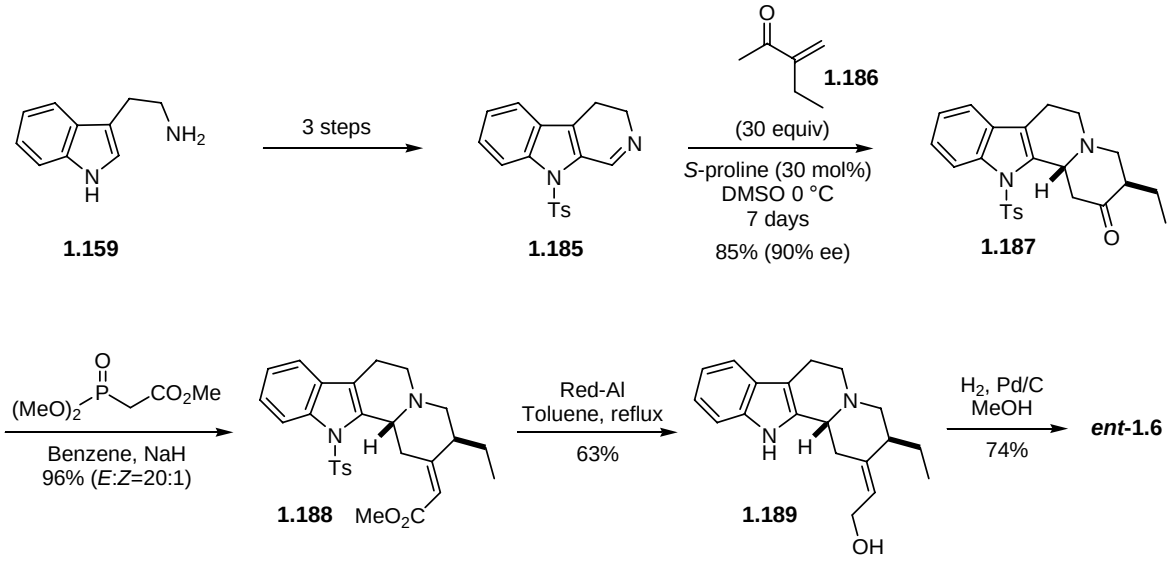


1.4.12 Itoh's Enantioselective Total Synthesis of *ent*-Dihydrocorynantheol (2006)

Itoh and co-workers recently reported an attractive enantioselective synthesis of *ent*-dihydrocorynantheol, which was published after we had completed our work in this area. Their approach relied on organo-catalysis to construct C(3)-substituted 1,2,3,4-tetrahydro-β-carboline derivatives in an enantioselective manner.[45] Tosyl protected carboline **1.185**, which was the substrate for the key step, was available in three steps

from tryptamine (Scheme 1.23). This material was exposed to the enamine derived from (*S*)-proline and 3-ethyl-2-butene-2-one to (**1.186**) give **1.185** in 85% yield and 90% *ee* with complete diastereoselectivity. It was not possible to draw any conclusions about the mechanism of the reaction since no intermediates could be isolated, but it was postulated that the reaction could proceed either via a hetero Diels-Alder mechanism or a Mannich-Michael-type pathway. However, the authors made the observation that the reaction works equally well using enamines derived from various methyl ketones, which undergo a Mannich reaction with **1.185** but cannot undergo the cyclization due to the lack of the enone functionality. This result suggests that the reaction of **1.185** with the enamine derived from **1.186** proceeds through a Mannich-Michael mechanism.

Scheme 1.23



With advanced intermediate **1.187** in hand, the synthesis was completed by performing a Horner-Wadsworth-Emmons reaction to furnish **1.188**, which upon exposure to Red-Al underwent reduction of the ester function to give the corresponding

alcohol **1.189** with concomitant deprotection of the tosyl group. Finally, the C(15) stereocenter was set through a diastereoselective hydrogenation to give *ent*-dihydrocorynantheol (***ent*-1.6**). By simply using (*L*)-proline instead of (*S*)-proline one should be able to obtain the correct absolute stereochemistry of the natural product. A potential drawback to Itoh's approach is that a large excess (30 equivalents) of enone **1.186** was needed in the key step, which would make the synthesis impractical on larger scale. Furthermore, even though an excess was used, this reaction required seven days at room temperature to go to completion. Nevertheless, Itoh's strategy resulted in the most concise enantioselective synthesis of *ent*-**1.6** requiring only seven steps from tryptamine.

1. 5 PRIOR ART IN THE MARTIN GROUP

We have had a long-standing interest in the development of general and efficient strategies for the synthesis of a wide variety of complex indole alkaloids. In particular, we have demonstrated the utility of ring-closing metathesis (RCM) as an extremely powerful construct in alkaloid synthesis, and we have expanded the scope of this useful transformation to allow access to a number of structurally diverse alkaloids.[46] After the initial disclosure by Grubbs and Fu in 1992 that RCM can be exploited to construct nitrogen-containing heterocycles from α,ω-dienes,[47,48] we rapidly capitalized on the tremendous utility of RCM. In fact, our application of RCM to the construction of the ABCE ring system of manzamine represents on of the first examples of RCM in complex alkaloid synthesis.[46a]

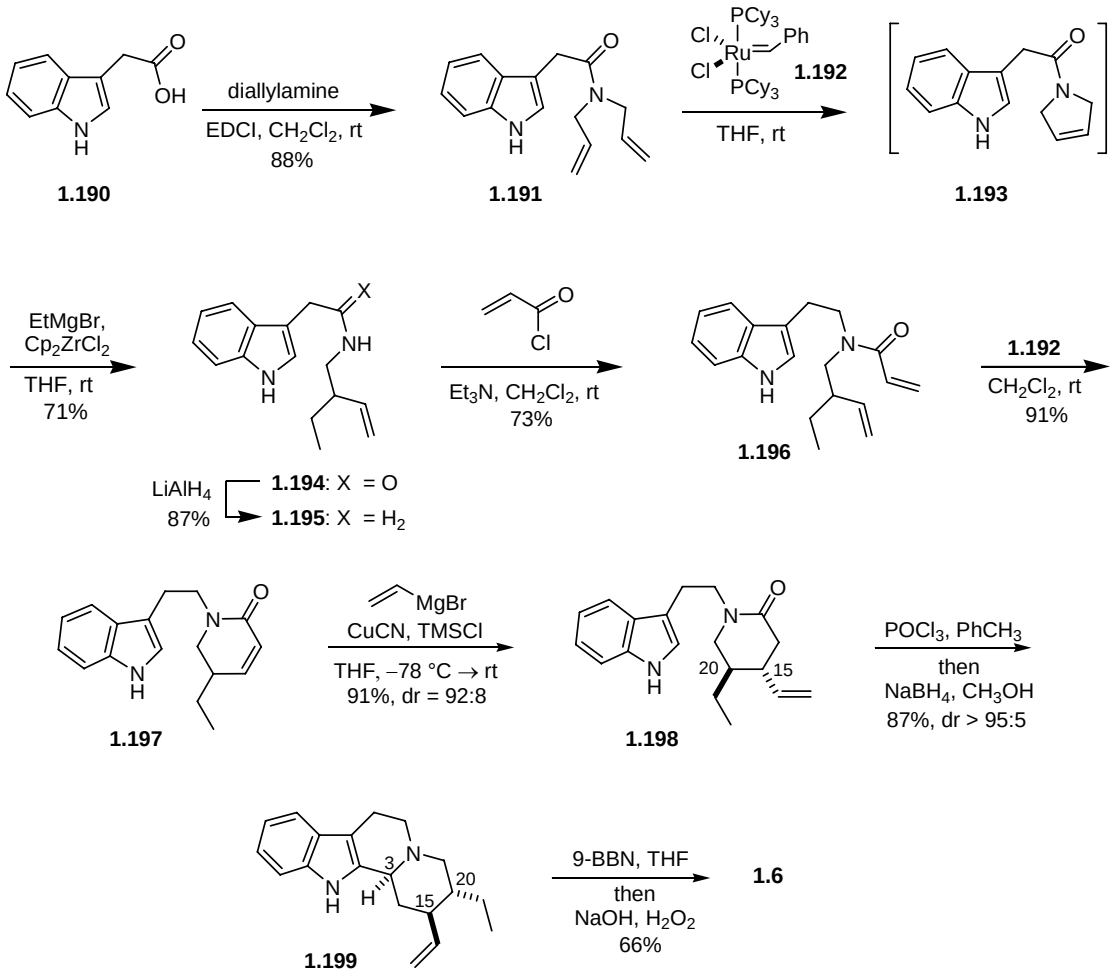
1.5.1 Diastereoselective Total Synthesis of Dihydrocorynantheol

In the context of our on-going efforts to apply and expand the scope of ring-closing metathesis towards alkaloid synthesis, we envisioned the potential of this transformation for the rapid construction of the D-ring of various corynanthe and oxindole alkaloids. In particular, an extremely concise route to dihydrocorynantheol (**1.6**) was developed using RCM as a key step.[49] Unlike our previous applications of RCM to alkaloid synthesis, this approach utilized RCM to fabricate α,β-unsaturated lactam that, in turn, could serve as a substrate for 1,4-additions of various nucleophiles, thus rapidly building up complexity while maintaining good control of relative stereochemistry.

As depicted in Scheme 1.24, the synthesis of **1.6** commenced with the EDCI-mediated coupling of indole-3-acetic acid (**1.190**) and diallylamine to give **1.191** in 88% yield. This material was then subjected to a one-pot RCM/zirconium catalyzed

carbomagnezation to afford **1.194** in 71% yield. The applications of carbomagnezations in natural product synthesis are rare,[50] and since this transformation can be carried out in an enantioselective fashion using chiral ligands,[51] the present strategy may readily adapted to provide dihydrocorynantheol enantioselectively. Reduction of the lactam function of **1.194** with $LiAlH_4$ and acylation of the resultant secondary amine with acryloyl chloride delivered **1.196**, thus setting the stage for a second RCM. In the event, exposure of **1.196** to Grubbs first generation catalyst **1.192** afforded the key α,β-unsaturated lactam **1.197** in 91% yield. This pivotal intermediate then served as a substrate for the critical 1,4-addition, and through the judicial selection of nucleophiles, two different alkaloids could be accessed from this common intermediate (*vide infra*).

Scheme 1.24



For the purpose of preparing dihydrocorynantheol, the 1,4-addition of a vinyl equivalent was studied in depth. It was eventually discovered that the cuprate derived from vinylmagnesium bromide and copper cyanide in the presence of TMSCl was an excellent nucleophile, which afforded the adduct **1.198** in 91% yield and 92:8 diastereomeric ratio. Having succeeded in the key 1,4-addition, the complete ABCD ring-system of **1.6** could be constructed through a Bishler-Napieralski reaction followed by a diastereoselective reduction of the resultant imine to give **1.198** in 87% yield as a single

diastereomer. Finally, the terminal olefin was subjected to a hydroboration with 9-BBN to deliver dihydrocorynantheol (**1.6**) in 67% yield. Thus, the natural product was prepared in 19% overall yield in only eight distinct chemical operations, which at the time of the publication of the preliminary communication represented the most concise and efficient approach to **1.6**.[52] It is also noteworthy that unlike many of the previous syntheses, excellent control of relative stereochemistry was achieved, and furthermore, no protecting groups were necessary through out the synthesis.

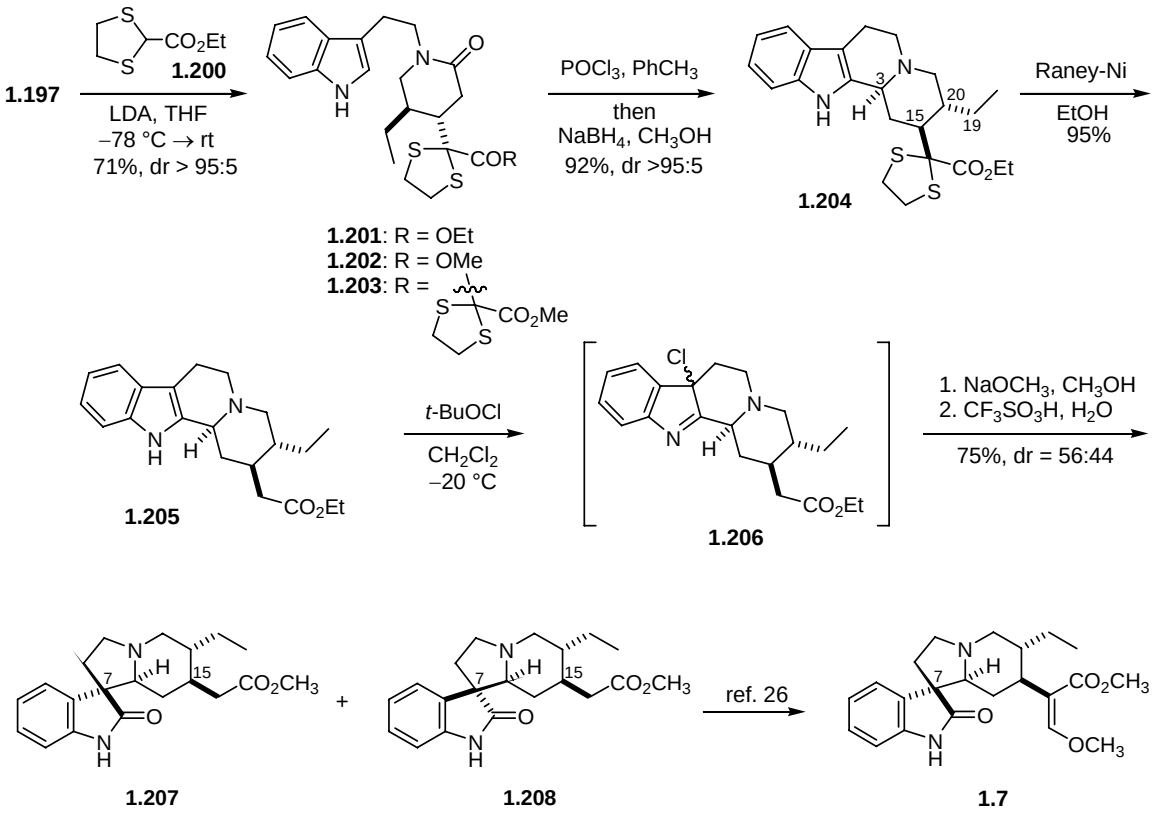
1.5.2 Formal Synthesis of Rhynchophylline and Iso-rhynchophylline

Encouraged by our successful 1,4-additions to the key intermediate **1.197** using cuprates, we next investigated the possibility of employing metal enolates as nucleophiles. It was envisioned that the introduction of a carbonyl function in the C(15) position could potentially allow for an efficient synthesis of the oxindole alkaloid rhynchophylline (**1.7**). A number of enolates including the lithium and sodium enolates of dimethyl malonate were explored. While the diastereoselectivity in these reactions were excellent, we were unable to obtain yields above 30%. We eventually discovered that 1,4-addition the lithium enolate of ethyl-1,3-dithilane-2-carboxylate (**1.200**) afforded **1.201** in good yield (71%) as a single diastereomer (Scheme 1.25). On the other hand, the 1,4-addition of the analogous methyl ester enolate, which would have represented a more direct route to rhynchophylline since the corresponding adduct **1.202** posseses a methyl ester, resulted in cross-Claisen reaction to generate preferentially β-ketoester **1.203**.

With intermediate **1.201** in hand, the C-ring was constructed via Bischler-Napieralski cyclization followed by highly diastereoselective imine reduction to deliver **1.204** in 92% yield and >95:5 diastereoselectivity. Following excision of the dithiolane in 95% yield using Raney-Ni, **1.205** was subjected to a three-step oxidative rearrangement

to deliver **1.207** and **1.208** in 75% yield, thus completing a formal synthesis of rhynchophylline (**1.7**) and iso-rhynchophylline (**1.8**).

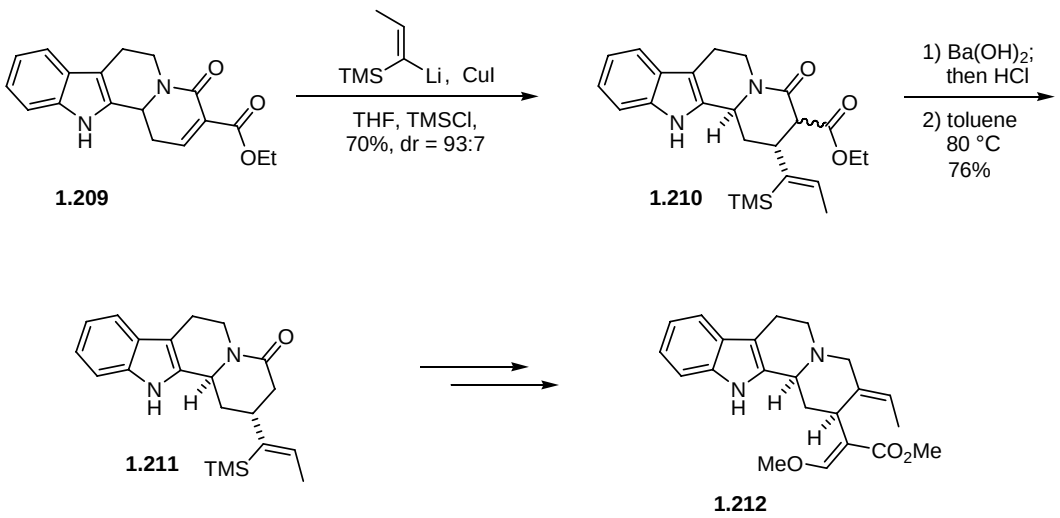
Scheme 1.25



1.6 EXTENDING THE SCOPE OF THE RCM/1,4-ADDITION STRATEGY TO INDOLOQUINOLIZIDINES: A POTENTIAL APPROACH TO HIRSUTINE AND RHYNCHOPHYLLINE

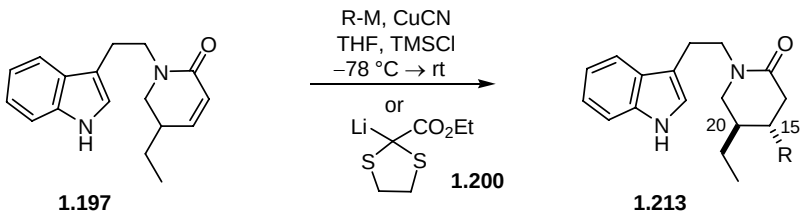
Over the past century, conjugate additions to various α,β-unsaturated carbonyl compounds has become one of the most important C-C bond forming reactions.[53] On the contrary, 1,4-additions to α,β-unsaturated amides and lactams are not as frequently utilized due to their lower reactivity relative to enones and enoates.[54] A number of examples of 1,4-additions to α,β-unsaturated piperidones have appeared in the literature.[55] However, the majority of these examples involve activation of the lactam by the incorporation of electron withdrawing groups either on the α-carbon or on the amide nitrogen as exemplified by the elegant synthesis of geissoschizine (**1.212**) by Overman and Robichaud (Scheme 1.26).[55d] Although this strategy renders the lactam more susceptible to 1,4-addition, the process typically adds steps to any given synthesis because of the need for the introduction and subsequent removal of these activating functionalities.

Scheme 1.26



As demonstrated in our approach to dihydrocorynantheol (**1.6**) and rhynchophylline (**1.7**) (*vide supra*), and as summarized in Table 1.1, we have shown that *unactivated* lactams such as **1.197** undergo stereoselective conjugate additions with the lithium enolate of ethyl-1,3-dithiolane carboxylate (**1.200**). Additionally, cuprates derived from Grignard reagents and copper(I) salts in the presence of TMS-chloride were found to be excellent nucleophiles.

Table 1.1

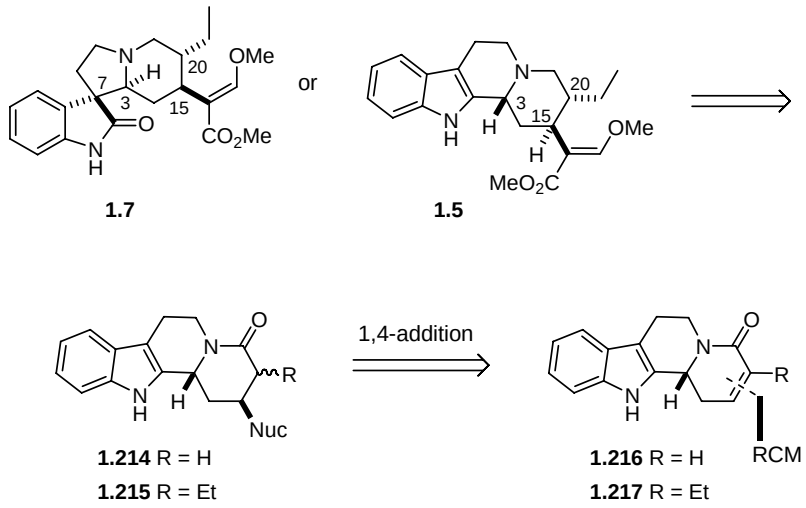


R-M	Yield (%)	dr
MgBr	91%	92:8
MgCl	99%	77:23
MgBr, $Si(CH_3)_3$	75%	>95:5
Li, CO_2Et, S, S	71%	>95:5

Given these results, we became intrigued by the possibility of extending the scope of the RCM/1,4-addition strategy to indoloquinolizidine-derived Michael acceptors such as **1.216** and **1.217** (Scheme 1.27). 1,4-additions to **1.197** and a subsequent Bischler-Napieralski cyclization resulted in a *cis* relationship between the hydrogens on the C(3) and C(15) positions. On the contrary, 1,4-addition to **1.216** should result in a C(3)-H / C(15)-H *trans* relationship based on the stereoelectronic preference for axial attack coupled with our prediction that the nucleophile should approach the Michael acceptor from the sterically less hindered face. As a consequence, 1,4-adducts such as **1.214** or **1.215** should be readily accessible, thus nicely mapping onto pseudo-corynanthe alkaloids such as hirsutine (**1.6**). Furthermore, a biogenetically inspired oxidative rearrangement of the indole to the corresponding oxindole would provide access to

spirooxindole alkaloids and could potentially allow us to develop a complimentary approach to rhynchophylline (**1.7**).

Scheme 1.27



There were a number of challenges that could be foreseen in this strategy. The most direct approach would be to utilize a Michael acceptor such as **1.217** in which the ethyl group had already been incorporated. In such an approach, however, one would have to overcome the additional steric hindrance imparted by the ethyl substituent in the 1,4-addition. On the contrary, if the introduction of the ethyl group were delayed until after the 1,4-addition, one would have to face the challenge of performing a diastereoselective alkylation of an exceedingly hindered amide enolate, and the literature precedence for such transformations was very limited.

1.7 CONCLUSION

For almost half a century, the structural challenges and significant biological activities of the corynanthe and oxindole alkaloids have inspired synthetic chemists to devise novel methodologies and clever tactics for their efficient syntheses. The ability to

control stereochemistry around the D-ring represents an interesting problem that has been addressed with varying degrees of success. While a significant amount of work has already been described in this area, these alkaloids still remain an important testing ground for new methods and strategies. Many of the approaches described above were either lengthy, non-selective, or did not readily lend themselves to the enantioselective preparation of these materials. However; a few stand out as quite impressive such as Meyers' enantioselective, 13-step synthesis of dihydrocorynantheol (**1.6**) using a chiral formamidine lithiation strategy to control the stereochemistry at the C(3) position. Another example is Deiters and Martin's eight step synthesis of racemic **1.6** using a highly efficient tandem RCM/carbomagnesation protocol as well as a RCM/1,4-addition strategy, which is readily adapted to allow for an enantioselective synthesis of **1.6**. Finally, Itoh's seven step enantioselective synthesis of *ent*-**1.6** using an elegant organocatalytic enamine addition to a tetrahydro-β-carboline derivative showcases the current state-of-the art in efficiency and selectivity in organic synthesis.

Form the discussion in this chapter it should be apparent that the synthetic approaches to hirsutine (**1.5**) and rhynchophylline (**1.7**) are significantly less refined as compared to those of dihydrocorynantheol (**1.6**). The major problem with all of these approaches is the low overall yield, which is due either to non-selective steps, requiring the separation of near equimolar mixtures of diastereomers, or several inefficient transformations (<45% yield). Furthermore, only Brown and Tietze controlled absolute stereochemistry; however, Brown's approach was lengthy requiring 17 steps, and Tietze's synthesis (15 steps) relied on the separation of a mixture (1:1) of diastereomers. Tietze eventually addressed this issued with the development of a catalytic asymmetric reduction of imine **1.76**, but the transformations required to elaborate this material to the requisite key intermediate **1.66** were not reported.

Given the important biological activity of hirsutine and rhynchophylline, we felt the need to address the significant shortcomings of the previous synthetic approaches. In particular, we wanted to develop a synthesis that efficiently controlled stereochemistry around the D-ring, in addition to being readily adapted for the enantioselective syntheses of these alkaloids. Furthermore, these efforts would allow us to examine in depth the scope and limitations of our RCM/1,4-addition strategy that was used so successfully in the synthesis of dihydrocorynantheol. As discussed above, 1,4-additions to α,β-unsaturated carbonyl derivative represent an extremely useful tool in organic synthesis, but the analogous transformations with α,β-unsaturated lactams have primarily been limited to those bearing electron withdrawing groups on the amide nitrogen or the α-carbon. Hence, the development of conditions that would allow for 1,4-additions to unactivated lactams such as indoloquinolizidine derivatives **1.216** and **1.217** would be an important contribution. In particular, 1,4-additions to α,β-unsaturated lactams such as **1.217** bearing an inactivating alkyl substituent in the α-position have to the best of our knowledge not been demonstrated. In the event that this transformation cannot be achieved, we will need to introduce the C(20) ethyl substituent at a later stage of the synthesis. However; this would represent a significant challenge given the scarcity of literature precedence for the diastereoselective alkylation of lactams of such complexity. Our efforts toward solving these problems will be detailed in the following chapter.

Chapter 2: Formal Syntheses of Rhynchophylline and Hirsutine

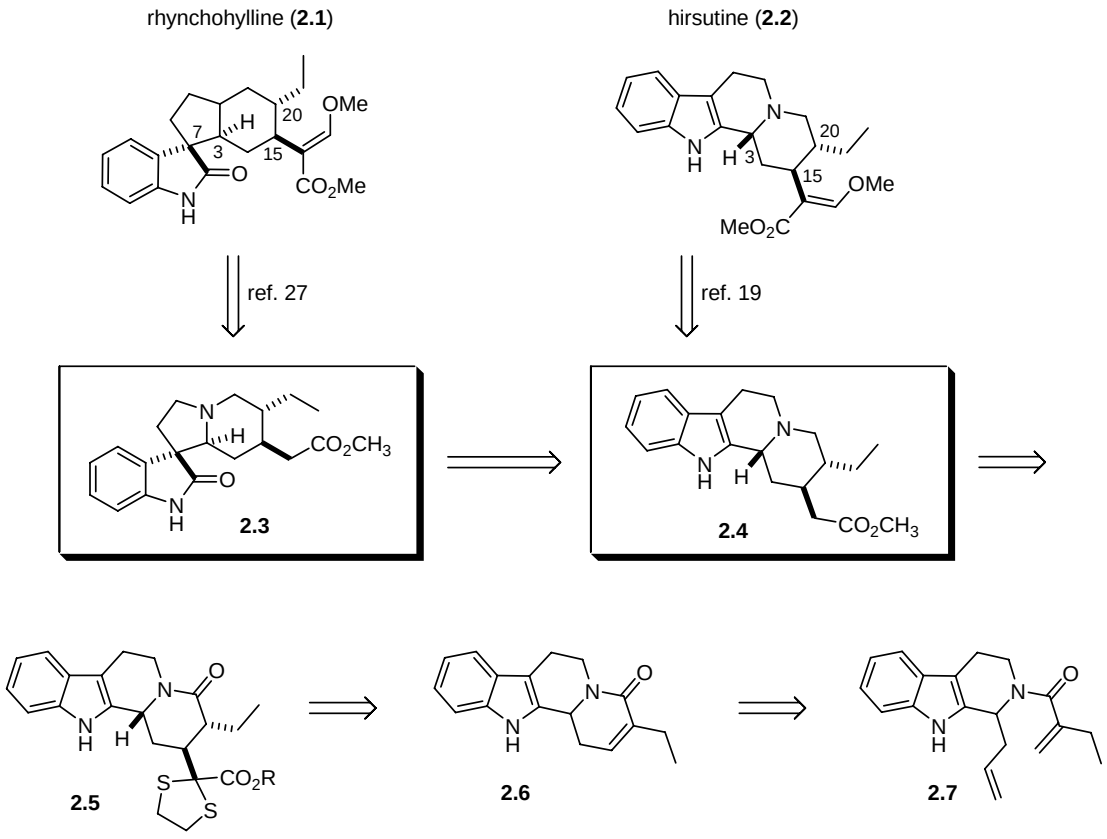
2.1 INTRODUCTION

The oxindole alkaloid rhynchophylline (**2.1**) and the pseudo-corynanthe alkaloid hirsutine (**2.2**) both possess valuable biological activity. In particular, **2.2** has been shown to be 11-20 times more potent against the influenza A virus (subtype H3N2) than the clinically used ribavarin.[5] As described in chapter 1, the previous synthetic approaches to **2.1** and **2.2** were relatively inefficient because of one or more low yielding transformations or the need to separate nearly equimolar mixtures of diastereomers. While addressing these issues, our goal was to expand the scope of the RCM/1,4-addition strategy, which had previously been developed in our group for the concise synthesis of dihydrocorynantheol (**1.6**), to include indoloquinolizidine derived Michael acceptors. Of particular interest was the 1,4-addition to α,β-unsaturated lactam **2.6** bearing an ethyl substituent in the α-position, since such transformations had not previously been described in the literature. The alternative strategy would involve the introduction of this substituent at a later stage of the synthesis; however, this would require the development of a diastereoselective alkylation of an exceedingly hindered lactam enolate

Thus, our initial retrosynthetic analysis of rhynchophylline and hirsutine is outlined in Scheme 2.1. We envisioned the target structure **2.3**, which has previously been converted to rhynchophylline (**2.1**),[27] as coming from indoloquinolizidine **2.4** via an oxidative rearrangement of the indole to the oxindole.[25] Preparation of the late stage intermediate **2.4** would also represent a formal synthesis of hirsutine (**2.2**), since **2.4** has previously been converted to **2.2** by Tietze and co-workers.[19] Indoloquinolizidine **2.4**, may be available in two steps from **2.5**, which in turn would result from the pivotal 1,4-

addition of the lithium enolate of ethyl 1,3-dithiolane carboxylate to α,β-unsaturated amide **2.6**. Finally, Michael acceptor **2.6** may be derived in five steps from tryptamine via **2.7** using ring-closing metathesis (RCM) as a key step (Scheme 2.1).

Scheme 2.1



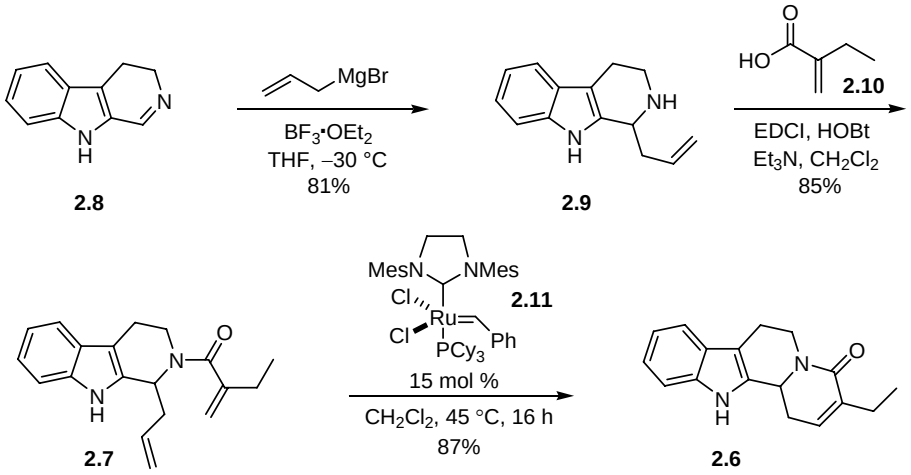
2.2 SYNTHESIS OF THE ETHYL-SUBSTITUTED MICHAEL ACCEPTOR 2.6

The synthesis of hirsutine (**2.2**) and rhynchophylline (**2.1**) commenced with the preparation of Michael acceptor **2.6**. Starting with tetrahydro-β-carboline **2.8**, which is available in two steps from tryptamine,[56] precomplexation of **2.8** with $BF_3{\cdot}OEt_2$ in THF at –30 °C for 10 min followed by the addition of allylmagnesium bromide (1 M solution

in Et_2O) provided the desired product **2.9** in 44% yield (Scheme 2.2). The first time the reaction was performed, it was allowed to warm to 10 °C, a tactic that resulted in the formation of a significant amount of an unidentified side product. However, if the reaction temperature was maintained at –30 °C for 2 h, followed by the addition of a saturated aqueous solution of $NaHCO_3$, the formation of the side product was suppressed and the desired product **2.9** could be isolated in 81% yield. This procedure was also convenient for scale up, and when performing the reaction on three-gram scale, the allylcarboline **2.9** could be readily isolated in 80% yield.

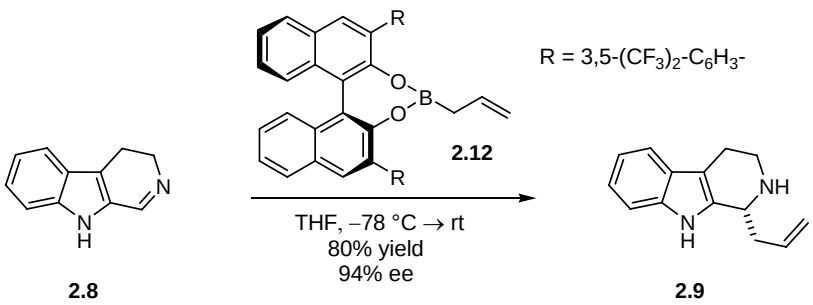
The resultant secondary amine function of **2.9** was then subjected to an EDCI-mediated amide bond coupling with the known 2-ethylacrylic acid (**2.10**)[57] to furnish RCM precursor **2.7** in 85% yield. With diene **2.7** in hand, we then began exploring the key RCM reaction using Grubbs 2nd generation catalyst (**2.11**). The reaction was found to be sluggish at room temperature, which is not surprising given that the RCM precursor **2.7** is not only electron deficient, but it is also 1,1-disubstituted. Nevertheless, after some experimentation we found that when running the reaction at 0.02 M concentration using 15 mol% **2.11** at 45 °C overnight, the desired product **2.6** could be isolated in 87% yield (Scheme 2.2).

Scheme 2.2



While **2.6** is a known compound,[58] the present synthesis, which provides **2.6** in only three steps and 60% overall yield from **2.8**, represents a significant improvement over previously published routes. It is also noteworthy that our approach readily lends itself to the enantioselective synthesis of **2.6**. In 1996, Nakamura and co-workers showed that one can perform asymmetric allylzincations to carboline **2.8** using bis-oxazoline ligands to afford **2.9** in 54% yield and 90% ee.[59] More recently, Chong and co-workers demonstrated an asymmetric allylboration to carboline **2.8**, which proceeded in 80% yield and 94% ee as depicted in Scheme 2.3.[60] Thus, while the racemic syntheses of hirsutine and rhynchophylline were initially targeted, the opportunity exists to achieve an enantioselective approach to these alkaloids.

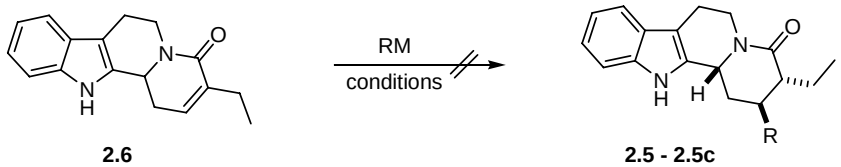
Scheme 2.3



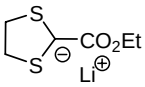
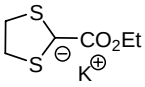
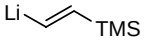
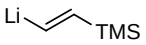
2.3 ATTEMPTED CONJUGATE ADDITIONS TO THE ETHYL-SUBSTITUTED MICHAEL ACCEPTOR 2.8

With the ethyl-substituted Michael acceptor **2.6** in hand, we then began to explore the key 1,4-addition. In spite of several attempts, including changing the counter ion, adding a Lewis acid, and heating the reaction, only starting material was recovered (Table 2.1). Conjugate additions of enolates such as the one derived from ethyl-1,3-dithiolane carboxylate are known to be reversible.[53a] It is therefore possible that the addition took place but that the steric bulk associated with the C(20) ethyl group promoted rapid retro-Michael reaction to afford the more thermodynamically stable starting materials.

Table 2.1



2.6 **2.5 - 2.5c**

Entry	RM	Cu(I) Source	Temp. (°C)	Solvents	Additive	Product	Result
1		-	–78 °C → rt	THF	-	**2.5**	83% rsm
2		-	–78 °C → rt	THF	$BF_3{\cdot}OEt_2$	**2.5**	84% rsm
3		-	60 °C	THF	-	**2.5**	90% rsm
4		-	–78 °C → rt	THF	-	**2.5**	94% rsm
5		CuI	–78 °C → rt	THF	TMSCl	**2.5b**	69% rsm
6		CuI	–78 °C → rt	Et_2O	TMSCl	**2.5b**	64% rsm
7		CuI	–78 °C → rt	THF	TMSCl	**2.5c**	81% rsm
8		CuI	–78 °C → rt	THF	$BF_3{\cdot}OEt_2$	**2.5c**	56% rsm

At this point, we turned our attention to the use of organocuprates (Table 2.1). There were no examples in the literature of 1,4-additions of cuprates to α,β-unsaturated lactams bearing an inactivating alkyl substituent in the α-position, although 1,4-additions of cuprates to lactams with an activating acyl substituent in the α-position are known.[55d] The use of trimethylsilylchloride to accelerate the reaction, which successfully effected 1,4-addition of cuprates to unsubstituted lactam **1.197**,[52] was attempted but without success. Addition of $BF_3{\cdot}OEt_2$, which is known to create a more reactive cuprate,[61] was also explored, but only starting material was isolated. A possible problem in these cuprate additions is that the added steric bulk exerted by the C(20) ethyl group as well as the

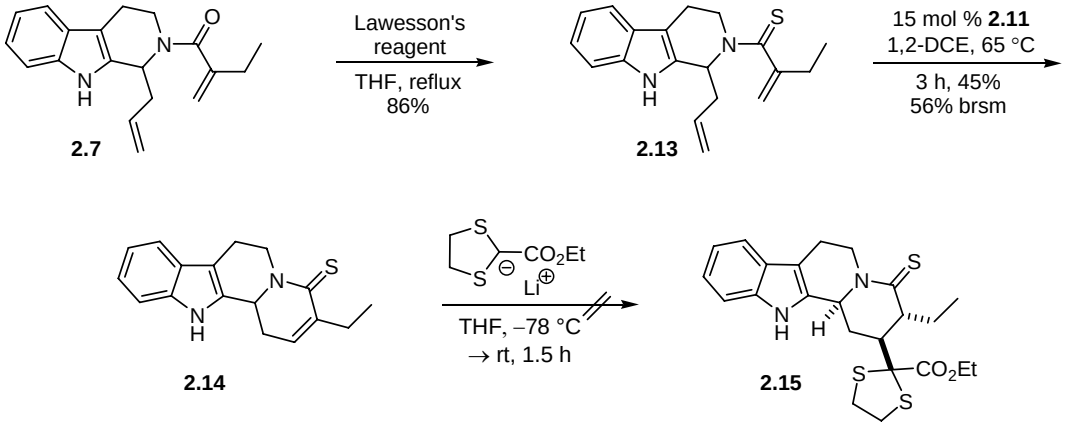
alkyl substituent on the amide nitrogen prevent simultaneous coordination of the cuprate reagent to both the carbonyl and the olefin.

2.4 SYNTHESIS OF, AND 1,4-ADDITION TO AN α,β-UNSATURATED THIOLACTAM

In an effort to render lactam **2.6** more susceptible toward conjugate addition, the corresponding thiolactam[13] was prepared since it has been reported that α,β-unsaturated thiolactams are better Michael acceptors than lactams.[11] The direct conversion of lactam **2.6** to thiolactam **2.14** was not attempted because α,β-unsaturated lactams are known to readily undergo deconjugation when treated with Lawesson's reagent.[62] Instead, **2.7** was converted to the corresponding thiolactam[63] **2.13** in 86% yield, and then subjected to **2.11** to affect the RCM (Scheme 2.4). Examples in the literature of α,β-unsaturated thiolactams undergoing RCM are rare. A likely problem in this transformation is that sulfur is known to poison the ruthenium catalyst **2.11**;[64] however, molecules containing sulfonamides[65] and dithianes[66] have successfully undergone RCM. The effects of catalyst loading, solvent, time, and temperature were studied, and it was eventually discovered that stirring a 0.2 M solution of **2.13** in 1,2-dichloroethane at 65 °C for 3 h in the presence of 15 mol % **2.11** provided the desired product in 45% yield (56% brsm).

With thiolactam **2.14** in hand, we turned our attention to the 1,4-addition using the lithium enolate of ethyl-1,3-dithiolane-2-carboxylate. Unfortunately, this reaction also failed to provide the desired product, and only starting material was isolated in each attempt. Again, the presence of the C(20) ethyl group is likely to be the main problem.

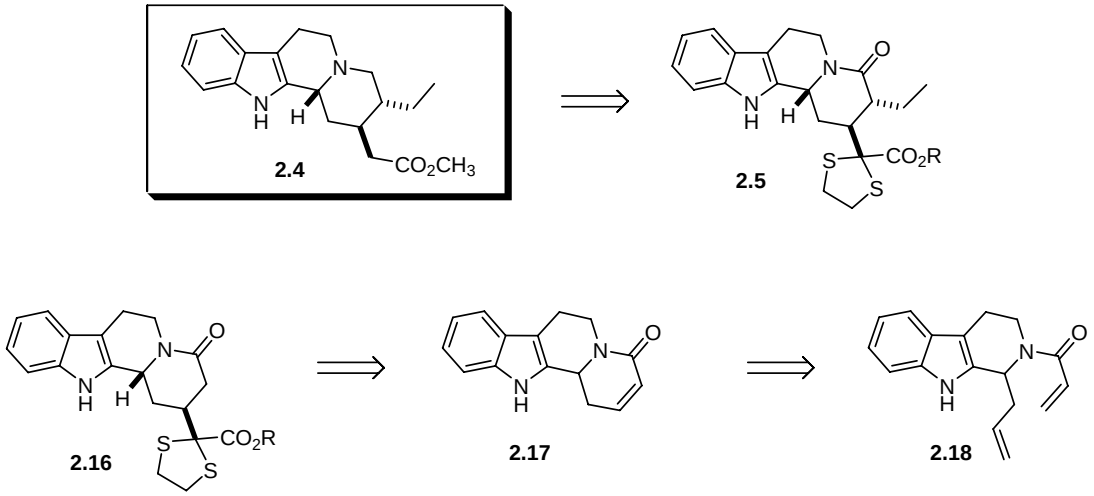
Scheme 2.4



2.5 CONJUGATE ADDITION/ALKYLATION APPROACH

At this point in the project it became clear that the initial approach, in which we proposed a 1,4-addition to Michael acceptor **2.6** bearing the C(20) ethyl group, was not going to be successful. As discussed in Chapter 1, the alternative was to delay the introduction of the C(20) ethyl group until after the conjugate addition. As shown in the revised synthetic plan outlined in Scheme 2.5, this would involve a 1,4-additon to the less sterically encumbered Michael acceptor **2.17**, which in turn would be available from diene **2.18** via RCM.

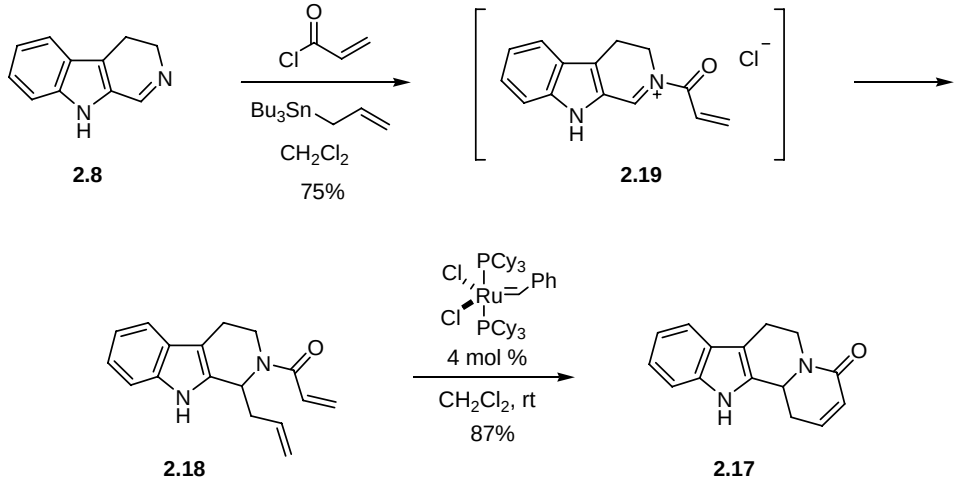
Scheme 2.5



The synthesis of **2.17**, which was initially described by Deiters,[49b] commenced with carboline **2.8** applying acyl iminium ion chemistry that has been frequently utilized in the Martin group (Scheme 2.6).[67] In the event, **2.8** was treated with acryloyl chloride giving rise to a transient acyl iminium ion **2.19**, which was readily engaged by the allyltributyltin that was already present in the reaction mixture. RCM precursor **2.18** was thus obtained in 75% yield in a one-pot operation. The ensuing RCM proceeded smoothly with Grubbs 1st generation catalyst **2.20** to furnish the requisite tetracyclic Michael acceptor **2.17** in only two steps from **2.8**.[68] Given the poor solubility of **2.17**, it was particularly convenient to avoid purification by chromatography. Instead, following removal of most of the solvent, the product crystallized directly from the reaction mixture upon cooling. Further trituration and recrystallization from CH_2Cl_2 / $CHCl_3$ furnished Michael acceptor **2.17** as a white powder in high purity. While lactam **2.17** is a known compound, previous syntheses were relatively long (six or seven steps) and proceeded in fairly low overall yield.[69] Our approach to **2.17**, which proceedes in two steps and 65%

overall yield from **2.8** therefore constitutes a marked improvement over previously published syntheses.

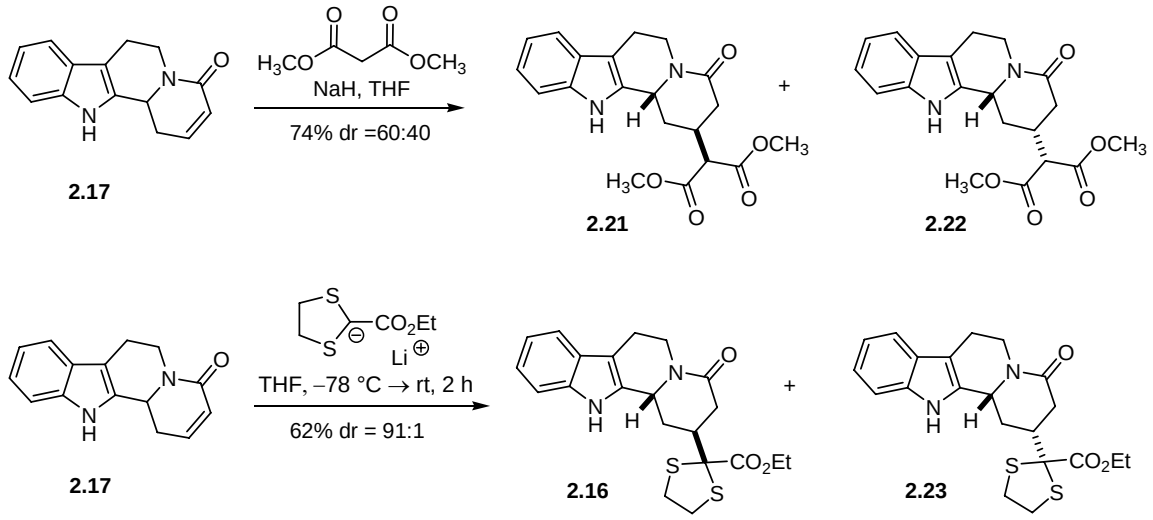
Scheme 2.6



Having developed a short and efficient route to tetracyclic Michael acceptor **2.17**, we began exploring its reactivity in the key 1,4-additions. The conjugate addition of the sodium enolate of dimethyl malonate to **2.17** required 48 h to reach completion but afforded the corresponding adduct in 74% yield (Scheme 2.7); however, the diastereoselectivity was low (dr = 60:40). On the contrary, 1,4-addition of the lithium enolate derived from ethyl-1,3-dithiolane-2-carboxylate to **2.17** proceeded in excellent diastereoselectivity (dr = 91:1) to furnish the expected adduct **2.16**, which could be readily isolated in 55-60% yield after facile removal of the minor diastereomer by chromatography. In order to obtain reproducible results in this reaction, it was necessary to deoxygenate the solvent through several freeze-pump-thaw cycles; however, even when this was done there was an erosion in the diastereomeric ratio upon scaleup. The stereochemical configuration of the major diastereomer **2.16** was tentatively assigned as *trans* between C(3)-H and C(15)-H protons. This assignment was based on the

stereoelectronic preference for axial attack during 1,4-additions as well as to the expectation that the dithiolane enolate should approach the α,β-unsaturated lactam from the convex face. This analysis was eventually corroborated at a later stage in the synthesis by obtaining an X-ray structure of **2.33** (*vide infra*).

Scheme 2.7

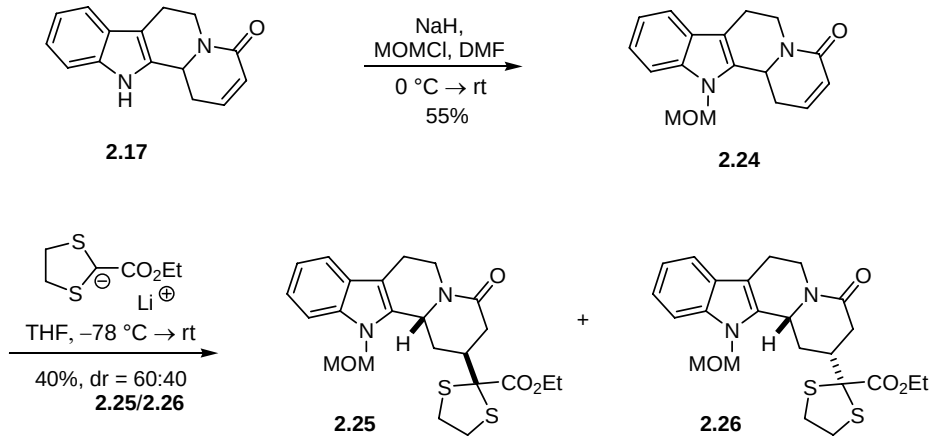


2.6 INTRODUCTION OF C(20) ETHYL GROUP VIA ALKYLATION

After finally achieving success in the difficult introduction of the C(15) substituent via 1,4-addition, the next challenge involved a diastereoselective alkylation to introduce an ethyl group at the C(20) position. It was anticipated that this would not be a trivial transformation due to the significant steric hindrance of the enolate derived from **2.16**. In preliminary experiments, all attempts to generate a dianion and selectively alkylate the more reactive α-carbon resulted in concomitant and unavoidable alkylation of the indole nitrogen. A possible solution to this problem involved protection of the indole nitrogen. We reasoned that by introducing a protecting group prior to the 1,4-addition it

may be possible to perform the addition and the alkylation in the same pot. Toward this, end the indole nitrogen of **2.17** was protected with a MOM group, which is a common indole protecting group, to furnish **2.24** in 55% unoptimized yield (Scheme 2.8). However, the ensuing 1,4-addition not only furnished the expected adduct **2.25** in low yield (40%), but also in poor diastereoselectivity (dr = 60:40).

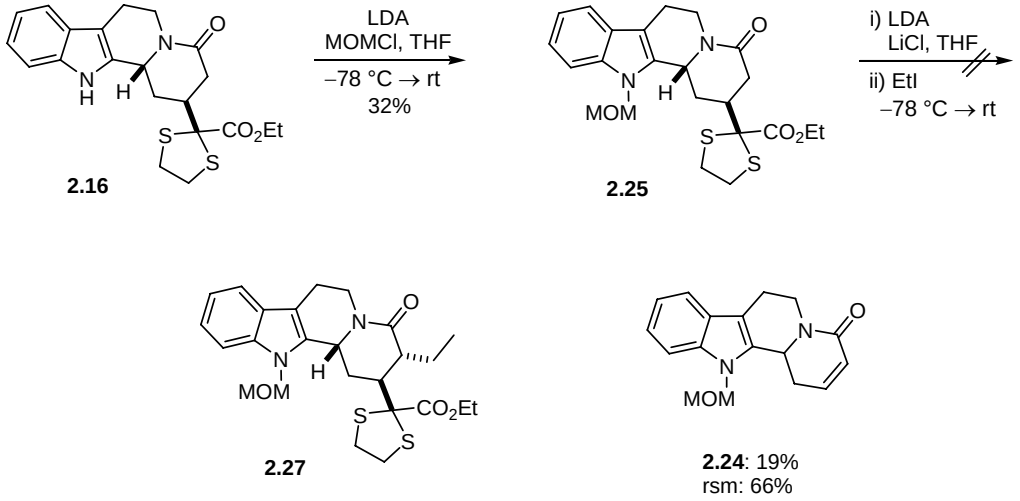
Scheme 2.8



Based on the aforementioned results, a step-wise approach involving 1,4-addition to the unprotected Michael acceptor **2.27**, followed by protection and alkylation appeared to be the best path forward to ensure optimal yield and diastereoselectivity. Protection of the Michael adduct **2.16** with MOMCl/NaH was examined, but this reaction proceeded in low yield (32%, Scheme 2.9). Nevertheless, sufficient quantities of **2.25** were obtained to explore the key alkylation step. In the event, **2.25** was deprotonated with LDA, and the resultant enolate was treated with excess ethyl iodide at –78 °C. Because no alkylation product **2.27** was observed, the reaction was allowed to warm to room temperature. This tactic, however, induced a retro-Michael reaction to afford **2.24** in 19% yield in addition to 66% recovered starting material (Scheme 2.9). This experiment suggests that the

lithium enolate derived from **2.16** is not sufficiently reactive to undergo allylation with ethyl iodide.

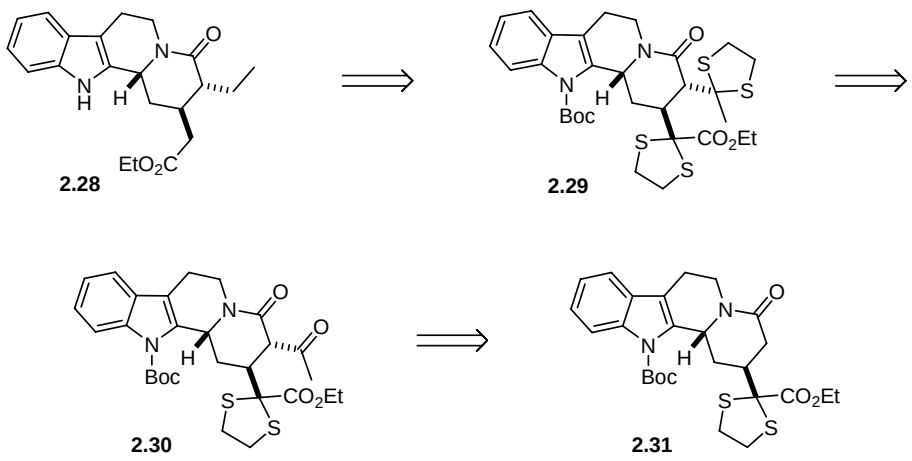
Scheme 2.9



2.7 ACYLATION APPROACH

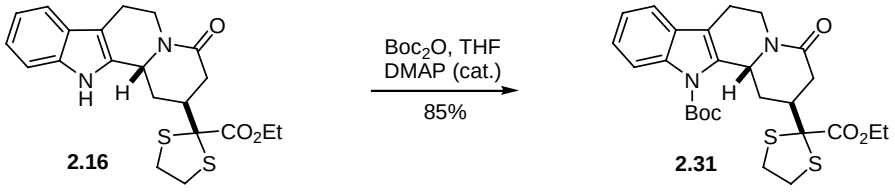
Because of the significant problems that were encountered during the initial attempts to introduce the C(20) ethyl substituent via alkylation, we opted to explore an alternative route. As shown in Scheme 2.10, the late stage intermediate **2.28** was envisioned as coming from bis-dithiolane **2.29** via reduction with Raney-nickel. Dithiolane **2.29** would be available from the β-keto amide **2.30**, which in turn may be accessed from **3.31** via acylation with a suitable acylating agent.

Scheme 2.10



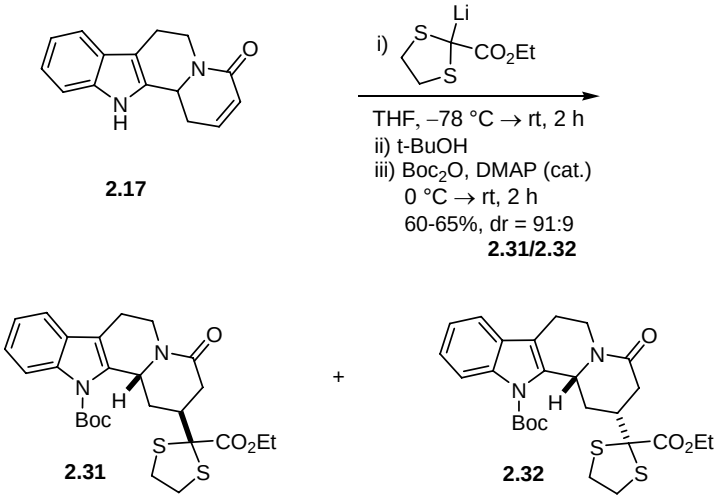
Before efforts toward the introduction of the C(20) acyl-group could commence, a suitable protecting group for the indole nitrogen had to be identified. While MOM is a fairly common indole protecting group, it could only be introduced in low yield (*vide supra*). Although protection with a silyl group was attempted, treating **2.16** in CH_2Cl_2 with TBSCl and NaH at 0 °C did not afford even a trace of the desired product. Only starting material was observed (51% isolated) along with substantial amounts of baseline material (TLC solvent: 3:1 EtOAc/hexanes) that was not isolated. Presumably the TBS group is too bulky to be introduced onto the hindered indole nitrogen of **2.16**, or alternatively, the resultant TBS protected indole may be too labile. On the contrary, a Boc group could be introduced in excellent yield (85%) simply by stirring **2.16** in THF in the presence of Boc_2O and a catalytic amount of DMAP (Scheme 2.11).

Scheme 2.11



Because of the ease by which the Boc protecting-group could be installed on the indole nitrogen, the opportunity arose to develop a one-pot conjugate addition/indole protection protocol. Such a procedure would have the benefit of avoiding the isolation and purification of Michael adduct **2.16**, which was somewhat inconvenient due to its poor solubility in most common organic solvents such as EtOAc and CH_2Cl_2. In the event, the 1,4-addition was carried out as described earlier (*vide supra*), and after the starting material had been consumed, the reaction mixture was cooled to 0 ˚C, and 1.1 equivalent of *t*-BuOH was added to ensure that the indole was fully protonated. Boc_2O and DMAP were then added directly to the reaction mixture, resulting in the formation of **2.31** and **2.32,** which could be isolated in 60-65% yield (Scheme 2.12). Unfortunately, the two diastereomers have identical R_f and could not be separated by chromatography. As a result, it was more convenient to carry out the two reactions in a stepwise fashion, and separate the diastereomers prior to the Boc-protection step.

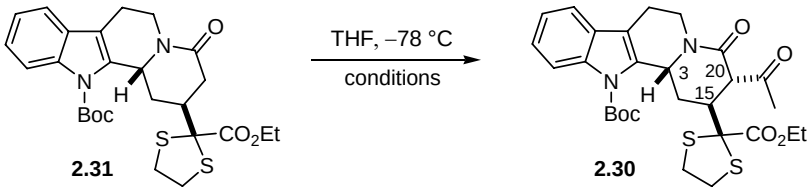
Scheme 2.12



With an ample supply of Boc-protected Michael adduct **2.31** in hand, our efforts were directed toward introducing the C(20) substituent via acylation. Deprotonation of

2.31 with LDA followed by acylation of the enolate with dimethylcarbonate according to the procedure of Beak[70] afforded the desired product **2.30** in a modest yield of 25%, although **2.30** could not be isolated cleanly. A more promising procedure involved the deprotonation of **2.31** with KHMDS in the presence $MgBr_2$-OEt_2, followed by addition of acetyl chloride according to a protocol exploited by Gammill[71] to provide **2.30** in 39% yield along with 8% recovered starting material. By increasing the amount of base and acylating agent from 1.5 equiv. to 3 equiv., the yield of **2.30** could be increased to 60% (Table 2.2). The product was obtained as a single diastereomer, and an nOe contact between H(3) and H(20) suggested that these hydrogen atoms were on the same side of the ring. Thus, β-ketoamide **2.30** most likely posses the requisite stereochemical configuration as depicted in Table 2.2.

Table 2.2



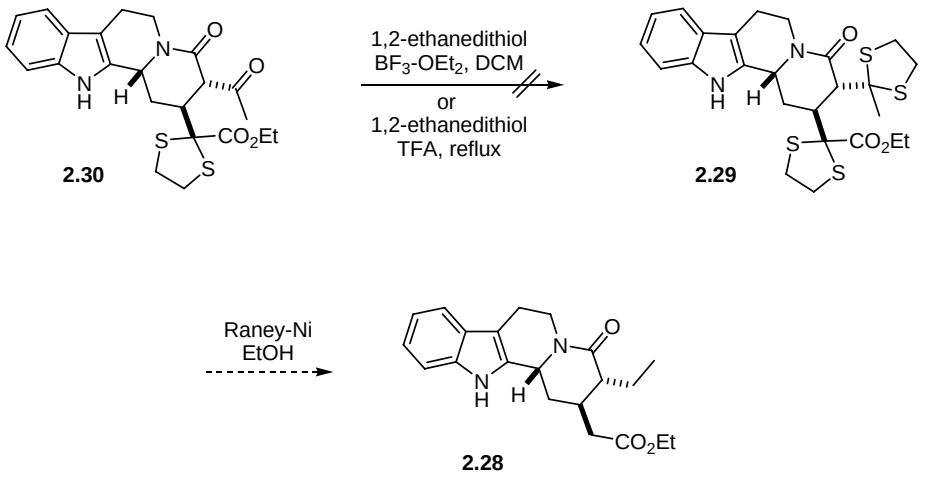
2.31 **2.30**

Entry	Base	Lewis acid	Acylating agent	Yield (%)
1	LDA (1.5 eq.)	-	MeOAc	25
2	KHMDS (1.5 eq.)	MgBr·OEt (1.1 eq.)	AcCl (1.5 eq.)	28
3	KHMDS (3 eq.)	MgBr·OEt (1.1 eq.)	AcCl (3 eq.)	60

The next step in the sequence involved the removal of the carbonyl oxygen of the acetyl group of **2.30** through the conversion to the bis-dithiolane **2.29** followed by reduction with Raney-nickel to afford **2.28** (Scheme 2.13). However, all efforts to introduce the dithiolane moiety were unsuccessful. For example, treating **2.30** with 1,2-

ethanedithiol/$BF_3 \cdot OEt_2$ in CH_2Cl_2[72] resulted only in the loss of the Boc group. Refluxing **2.30** in TFA and 1,2-ethanedithiol[73] resulted in a complicated mixture of products that was not separated.

Scheme 2.13



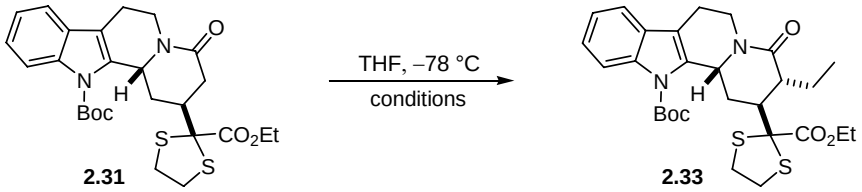
At this point in the project, preliminary success had been achieved in the alkylation of **2.31**, which was being pursued concurrently with the acylation studies. Since the introduction of the ethyl substituent via alkylation would result in a synthesis that is one step shorter, the acylation approach was abandoned, and no further attempts were made to convert **2.30** to **2.29**.

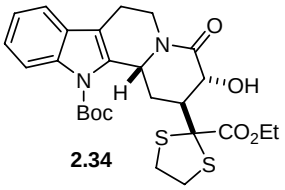
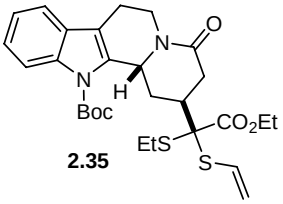
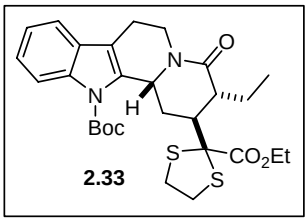
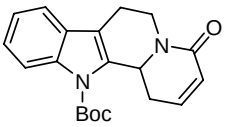
2.8 RETURNING TO THE ALKYLATION APPROACH

Having established an efficient approach to the protected Michael adduct **2.31**, we decided to reinvestigate the possibility of introducing the ethyl substituent via alkylation. Preliminary experiments using LDA and an excess of EtOTf resulted of the destruction of the dithiolane moiety as well as loss of the Boc group. Therefore, we turned to the milder

alkylating agent EtBr as shown in Table 2.3. Interestingly, while none of the desired product **2.33** could be isolated, compound **2.34**, in which a hydroxyl group had been incorporated in the C(20) position, was obtained in 26% yield as a single diastereomer along with 46% recovered starting material (entry 1). It was hypothesized that dissolved oxygen in the solvent was responsible for the α-oxidation of the enolate. The solvents were therefore degassed using the freeze-pump-thaw method immediately prior to use for all subsequent reaction; this tactic solved the α-oxidation problem.

Table 2.3



entry	base	RX	solvent/additives	results	
1	LDA (2 eq.)	EtBr (6 eq.)	THF	26% **2.34** 46% rsm	 **2.34**
2	KHMDS (1 eq.)	EtI (2 eq.)	THF/HMPA[a] 3:1	67% **2.35** 16% rsm	 **2.35**
3	KHMDS (2 eq.)	EtI (4 eq.)	THF/toluene	36% 2.33 17% rsm	
4	**NaHMDS (2 eq.)**	**EtI (4 eq.)**	**THF/toluene**	**48% 2.33** **22% rsm**	 **2.33**
					 **2.36**

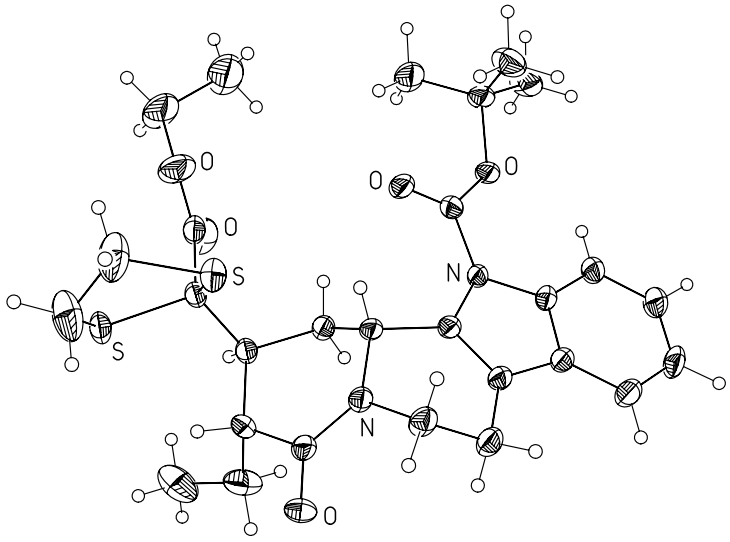
[a] HMPA was added after deprotonation with KHMDS

After discovering and eliminating the problem of α-oxidation, the next challenge was to find conditions that would effect the alkylation without destroying the dithiolane moiety. Toward this end, the reactivity of the enolate was increased by deprotonation with KHMDS to generate the potassium enolate followed by the addition of HMPA. The enolate was then subjected to the more reactive electrophile EtI, but none of the desired

product **2.33** was obtained. Instead, product **2.35** was isolated in 67% yield as a mixture of diastereomers along with 16% recovered starting material. The dithiothioether **2.35** can be thought of as arising from cleavage of the dithiolane ring via E_2 elimination under the strongly basic conditions,[74] followed by alkylation with ethyl iodide. Gratifyingly, after considerable experimentation it was eventually discovered that the desired product could be obtained by increasing the amount of KHMDS and EtI, and running the reaction in the absence HMPA. These conditions afforded the requisite product **2.33** in 36% yield along with 17% unreacted starting material (entry 3). The low yield and mass balance can be attributed to the formation of a number of side products including **2.35**.

An X-ray structure of alkylation product **2.33** was obtained in order to establish the stereochemistry of the alkylation as well as of that of the 1,4-addition (Figure 2.1). Gratifyingly, the crystal structure indicated that the 1,4-addition step had indeed resulted in a *trans* relationship of C(3)-H/C(15)-H, which is the product resulting from axial attack. Furthermore, the alkylation had occurred from the opposite face of the C(15)-substituent, resulting in the requisite stereochemistry for pseudo-corynanthe alkaloids such as hirsutine (**2.2**). The X-ray analysis also offered insight into the difficulties associated with the alkylation of **2.31**. Lactam **2.33** shown in Figure 2.1 is extremely sterically congested. The X-ray structure reveals that there is a severe steric interaction between the Boc-protecting protecting group and the C(15) dithiolane substituent. This steric interaction may account for why **2.31** shows such a high propensity for undergoing a retro-Michael reaction.

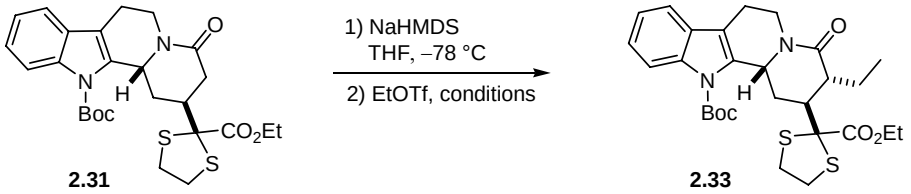
Figure 2.1 ORTEP plot of **2.33**. Displacement ellipsoids are scaled to the 50% probability level.



The choice of enolate counter ion was found to be critical. The lithium enolate was not sufficiently reactive to undergo alkylation with EtI at −78 ˚C (see Scheme 2.9), whereas the more reactive potassium enolate gave a number of side products along with the desired alkylation product **2.33**. The use of the sodium enolate of **2.31**, however, resulted in a much cleaner reaction, and a significantly improved yield (entry 4). Thus, deprotonation of **2.31** with 2 eq. NaHMDS followed by the addition of 4 eq. EtI gave **2.33** in 48% yield as a single diastereomer along with 22% recovered starting material. All efforts to drive the reaction to completion through warming, using a larger excess of EtI, or prolonging the reaction time, resulted in a reduction in the yield as well as a reduction in the amount of recovered starting material. Furthermore, although the reaction was significantly cleaner than when using KHMDS as the base, several side products were still being formed. For instance, the ^{1}H NMR spectrum of the crude reaction mixture indicated the presence of dithioether **2.35** as well as **2.36** resulting from a retro-Michael reaction.

We reasoned that it may be possible to suppress the formation of these and other side reactions by lowering the temperature of the reaction to –100 ˚C. Since the alkylation with ethyl iodide was sluggish at –78 ˚C, we felt that a more reactive electrophile would be needed at –100 ˚C, and we therefore used EtOTf for all subsequent experiments. In the event, **2.31** was deprotonated with NaHMDS at –78 ˚C, and after stirring the mixture for 1 h at this temperature, the reaction was cooled to –100 ˚C, and EtOTf was added. The reaction was quenched after 30 min, and the desired product was isolated along with unreacted starting material in 29% and 59% yield respectively. The reaction was extremely clean as indicated by the ^{1}H NMR spectrum of the crude reaction mixture, which only displayed resonances corresponding to product and unreacted starting material. The R_f value of the product and the starting material were almost identical, and **2.31** and **2.33** were therefore not separated in these experiments but rather isolated as a mixture. By weighing the mixture, the yields of **2.31** and **2.33** were then easily determined by NMR integration (Table 2.4).

Table 2.4

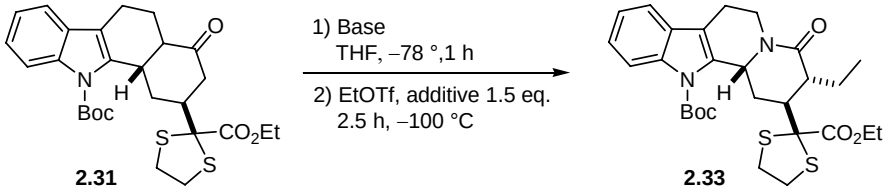


Entry	Conc. (M)	Eq. EtOTf	Additive	Time / temp (°C)	Yield (%)	RSM (%)
1	0.075 M	4	-	30 min, –100 °C	29%	59%
2	0.15 M	4	-	2.5 h, –100 °C	57%	33%
3	**0.15 M**	**4**	**DMPU, 1.5 eq.**	**2.5 h, –100 °C**	**70%**	**20%**
4	0.15 M	4	DMPU, 4.0eq.	2.5 h, –100 °C	66%	19%
5	0.15 M	8	DMPU, 1.5 eq.	2.5 h, –100 °C	67%	15%
6	0.15 M	4	DMPU, 1.5 eq.	15 min, –100 °C; 2.5 h, –78 °C	70%	9%

In order to optimize the yield in this alkylation, the concentration of the reaction was doubled, and the reaction time was extended to 2.5 h (entry 2). These changes increased the yield of **2.33** to 57% and reduced the amount of recovered starting material to 33%. In order to increase the reactivity of the enolate, DMPU (1.5 eq.) was added resulting in an increase in the yield of **2.33** to 70% (20% rsm), which was the best result obtained (entry 3). Repeated attempts to drive the reaction to completion, however, were fruitless. Increasing the amount of DMPU from 1.5 to 4 eq. (entry 4) or increasing the amount of EtOTf (entry 5) did not lead to any significant change in the yields of product and recovered starting material. Additionally, increasing the reaction temperature from –100 ˚C to –78 ˚C 15 min after the addition of electrophile did not increase the yield of **2.33** (entry 6), but the amount of recovered starting material was reduced to 9% due to the formation of side products that were not isolated.

With the hope of being able to drive the reaction to completion, the effect of varying the base was reinvestigated, and the results are summarized in Table 2.5; entry 1 shows the optimal conditions from Table 2.4 for the sake of comparison. An increase in the amount of base, however, led to slightly reduced yields of **2.33** (entries 2 and 3). It was also confirmed that sodium is indeed the optimal counter ion, as deprotonation with KHMDS (entry 4) led to a sharp decline in the yield of **2.33** (36%). Finally, the use of HMPA instead of DMPU was explored, but there was no noticeable difference between entry 5 and entry 2. After extensive experimentation, it was not possible to drive the reaction to completion even after rigorous exclusion of water. A possible explanation may be that the enolate of **2.31**, which is rather hindered, abstracts a proton from EtOTf via an E_2 elimination pathway. Another explanation could be that the alkylation product **2.33** could serve as a proton source to protonate **2.31**.

Table 2.5



Entry	base	Eq. EtOTf	Additive	Yield (%)	RSM (%)
1	**NaHMDS (2 eq.)**	**4**	**DMPU**	**70%**	**20%**
2	NaHMDS (3 eq.)	6	DMPU	68%	17%
3	NaHMDS (4 eq.)	8	DMPU	62%	22%
4	KHMDS (2 eq.)	4	DMPU	36%	36%
5	NaHMDS (4 eq.)	8	HMPA	62%	23%

The best conditions identified thus far (i.e. 2 eq. NaHMDS, 4 eq. EtOTf, 1.5 eq. DMPU, 2.5 h, −100 ˚C) were then applied to a larger scale reaction, and the product and the starting material were separated to determine the isolated yield of the reaction. As shown in Table 2.5, the reaction works well on larger scale, and the yields after chromatographic separation of product and starting material were virtually identical for the two experiments. One final and important note regarding the alkylation is the exceedingly high diastereoselectivity; only one diastereomer was observed in the ^{1}H NMR spectrum of the crude reaction mixture.

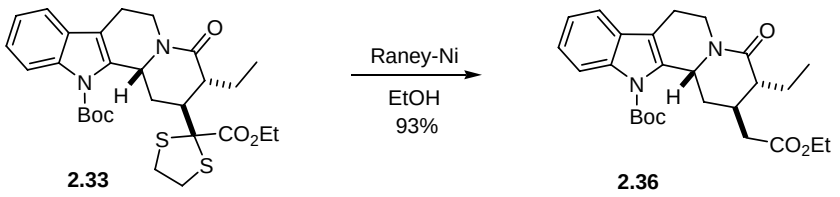
Table 2.6

Entry	Scale (mg **2.31**)	Yield (%)	RSM (%)
1	200 mg	67%	20%
2	240 mg	68%	22%

2.11 FORMAL SYNTHESIS OF HIRSUTINE

With alkylation product **2.33** in hand, the formal synthesis of hirsutine (**2.2**) could be completed in a relatively straightforward manner. The next step in the synthesis involved the removal of the dithiolane moiety. As depicted in Scheme 2.14, this was accomplished by stirring **2.33** in ethanol the presence of Raney-Nickel to afford **2.36** in excellent yield (93%).

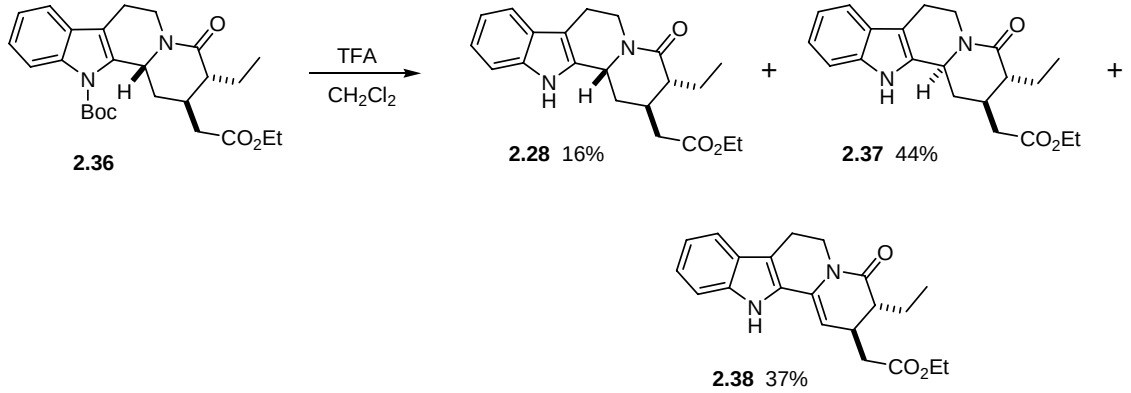
Scheme 2.14



2.33 **2.36**

At this point in the synthesis we elected to remove the indole protecting group (Scheme 2.15). In an initial experiment to deprotect the indole with TFA, no change in R_f was observed by TLC after stirring for 3 h. Additional TFA was added and the reaction was stirred at room temperature overnight. Analysis of the mixture indicated two new spots on the TLC plate in addition to a spot with the same R_f as the starting material. Following chromatographic separation of the three spots it was determined that all the starting material had indeed been consumed. In addition to the desired product **2.28** (which co-eluted with the starting material using 1:1 EtOAc/hexanes), a lower R_f product **2.37** was isolated and was assigned as the C-3 epimer based on its ^{1}H NMR, ^{13}C NMR, COSY, HMQC, LR-MS data. This result is not surprising given that indoloquinolizidine skeletons are known to be susceptible to C(3)-H epimerization under acidic conditions.[10] Additionally, a higher-R_f product **2.38** was isolated that was assigned as the product of auto-oxidation based on its ^{1}H NMR, ^{13}C NMR, LR-MS data (Scheme 2.15).

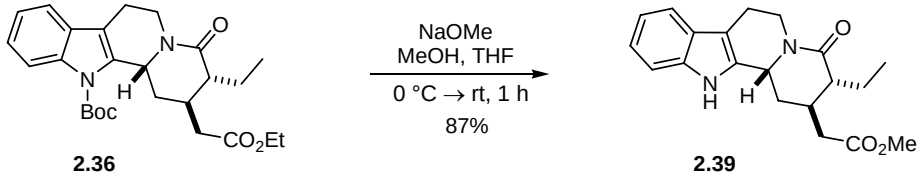
Scheme 2.15



This experiment demonstrates that **2.36** or the corresponding deprotected indole **2.28** are not stable. Although the formation of side products might be avoided by

reducing the reaction time, a different and more efficient approach was pursued. Thus, Boc-protected indole **2.36** was treated with NaOMe/MeOH in THF with the hope of cleanly removing the protecting group and effecting the transesterification to the requisite methyl ester (Scheme 2.16). Boc-deprotection of indoles with NaOMe has been reported to give low and inconsistent yields of product due to the fact that the deprotected indole is susceptible to oxidation in the 3-position during the basic reaction conditions.[75] However, when performing the reaction in degassed THF using a freshly prepared solution of NaOMe prepared from degassed MeOH, the reaction worked nicely. As expected, the reaction proceeded with concomitant transesterification to afford methyl ester **2.39** in 87% yield, which was readily isolated in high purity by a single crystallization.

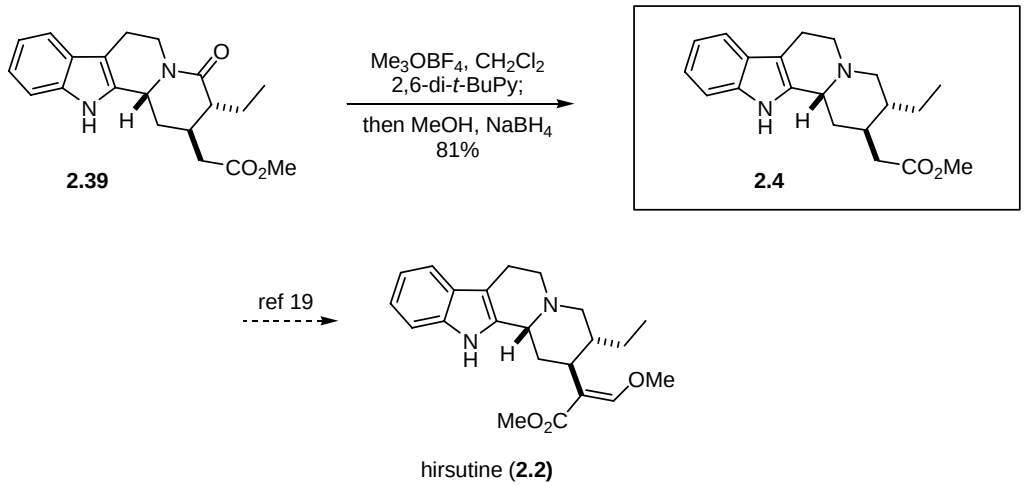
Scheme 2.16



2.36 **2.39**

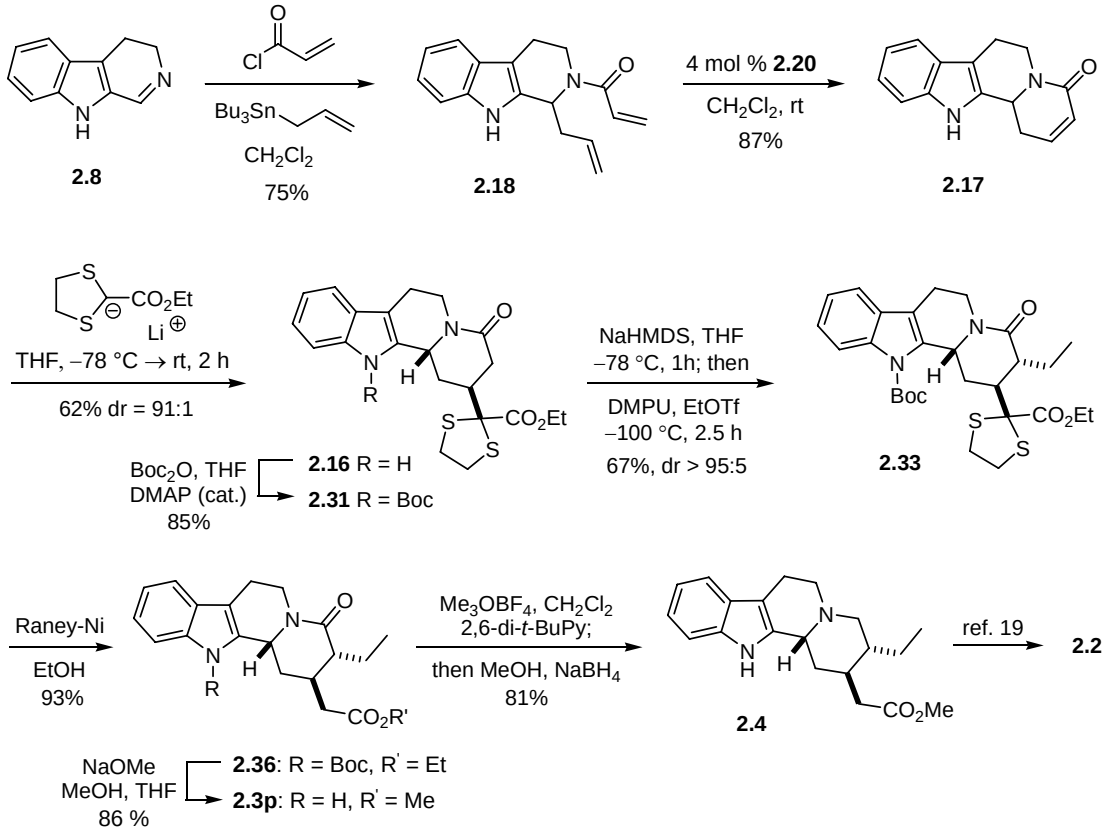
Following deprotection/transesterification, the final step in the formal synthesis of hirsutine (**2.2**) involved the reduction of lactam **2.39** to the indoloquinolizidine **2.4**[76] (Scheme 8). In the event, exposing **2.39** trimethyloxonium tetrafluoroborate and 2,6-di-*t*-butylpyridine followed by reduction of the resultant iminium ion with $NaBH_4$ according to a published procedure[77] furnished the target indoloquinolizidine **2.4** in 81% yield the NMR data of which was in full agreement published ^{1}H NMR data.[78]

Scheme 2.17



In order to obtain a good yield in the reduction, it was important to ensure high purity of lactam **2.39**. Furthermore, the indoloquinolizidine **2.4** was found to be unstable to air, and the crude material readily decomposed when exposed to the atmosphere for a few hours. This problem could be avoided by simply purifying the crude reaction mixture immediately following the workup. Thus, the synthesis of **2.4**, which is shown in its entirety in Scheme 2.18, completes the formal synthesis of hirsutine **2.2**, since **2.4** has previously been converted to **2.2** in two additional steps.[19]

Scheme 2.18

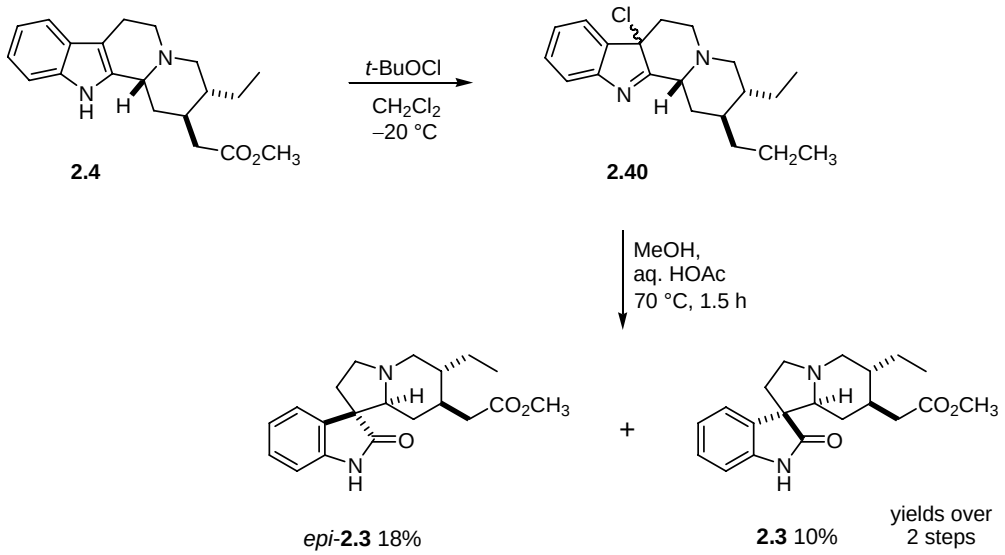


2.12 FORMAL SYNTHESIS OF RHYNCHOPHYLLINE

A formal synthesis of the oxindole alkaloid rhynchophylline (**2.1**) was achieved via the oxidative rearrangement of **2.4** to give oxindoles **2.3** and *epi*-**2.3**. This transformation was first attempted using a two-step procedure[79] in which **2.4** was first chlorinated with *t*-BuOCl to give. Following removal of the solvent, **2.40** was dissolved in a mixture of MeOH and aqueous acetic acid and heated to 70 ˚C to effect the rearrangement to a spirocyclic imidoether followed by hydrolysis to provide **2.3** and *epi*-**2.3** (Scheme 2.19). After aqueous workup and chromatographic separation, oxindoles **2.3** and *epi*-**2.3** were isolated in 10% and 18% respectively. The low yield of the one pot

procedure can be attributed to the formation of several side products that were difficult to separate from the desired spiro-oxindoles.

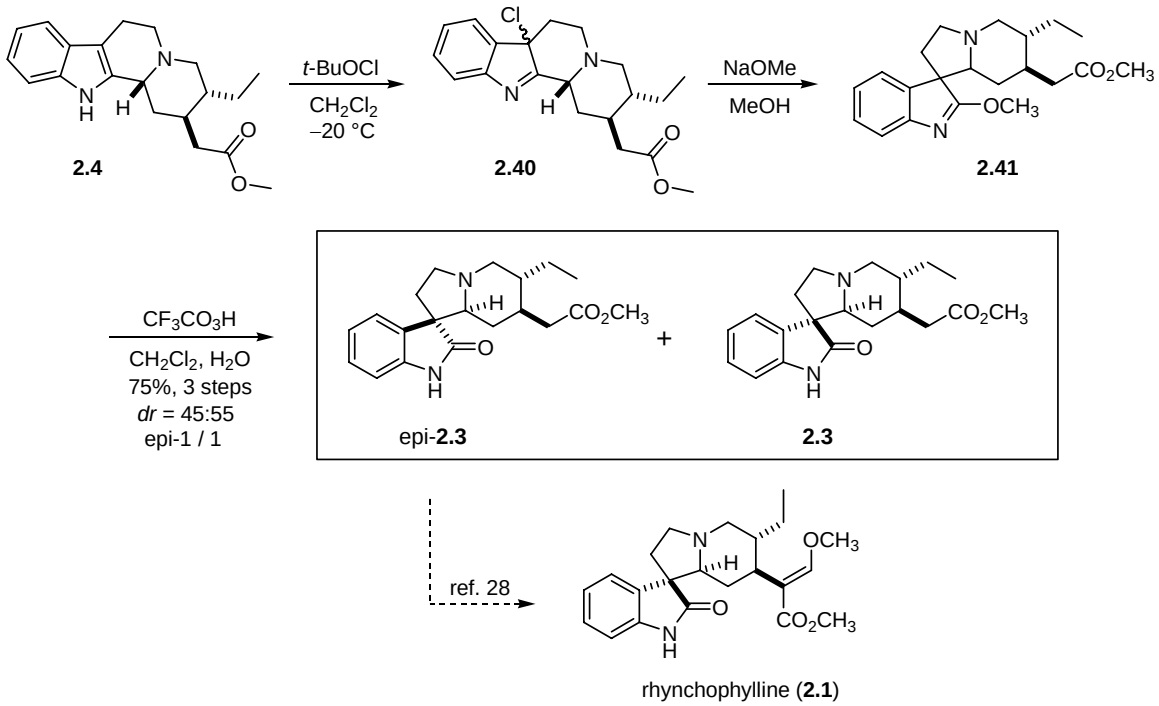
Scheme 2.19



In order to improve the yield of the oxidative rearrangement, an alternative procedure was investigated in which the 1,2-rearrangement and the hydrolysis were conducted in separate steps. The conversion of corynanthe alkaloids to their corresponding oxindoles using this tactic has been extensively investigated by Acklin and co-workers,[24] and has also been employed by Martin and co-workers.[26,49b] Thus, **2.4** was exposed to *t*-BuOCl to effect the chlorination of the C(3) position. Following removal of the solvent, the residue was treated with NaOMe/MeOH to effect the pinacol-type rearrangement to give spirocyclic imidoether **2.40** (Scheme 2.20). This intermediate was then hydrolyzed under acidic condition in a separate step to afford the desired oxindoles. Using this procedure, the desired oxindoles **2.3** and *epi*-**2.3**, which are epimeric at C(7), could be isolated in good yield (39% and 37% respectively over the three steps). The ^{1}H

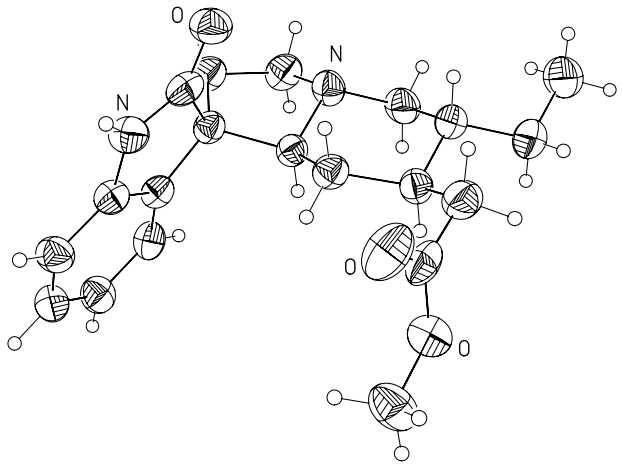
NMR data of **2.3** and epi-**2.3,** and the melting point of **2.3,** were in good agreement with those reported in the literature.[27]

Scheme 2.20



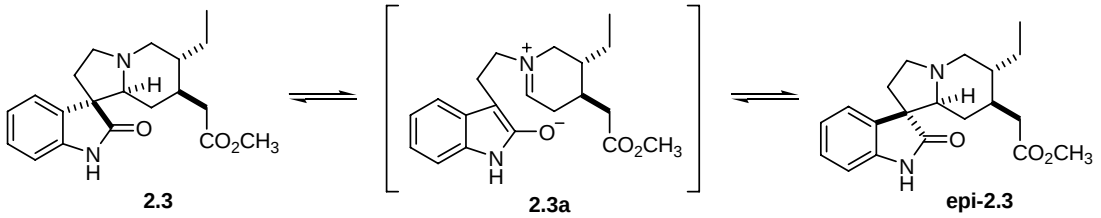
Ban and co-workers assigned the stereochemistry of the lower R_f C(7) epimer as oxindole **2.3**, and we were able to verify this structural assignment, through single crystal X-ray analysis (Figure 2.3). This reveals a mistake in a structural assignment in an earlier paper, which claims the synthesis of **2.3**.[80]

Figure 2.2 ORTEP plot of **2.3**. Displacement ellipsoids are scaled to the 50% probability level.



The C(7)-epimers **2.3** and epi-**2.3** are readily separated by chromatography; however, they are not configurationally stable. In fact, they readily interconvert under acidic or basic conditions via a retro-Mannich/Mannich pathway that is frequently observed with spiro-(pyrrolo-3,3'-oxindoles) (Scheme 2.21).[27] Although one could envision the possibility of advancing either **2.3** and epi-**2.3** to their corresponding natural products, Ban and co-workers elaborated epi-**2.3** into both epi-**2.1** and **2.1** and in two and three steps, respectively.[27] Our approach to epi-**2.3** therefore represents a formal synthesis of **2.1** and epi-**2.1**.

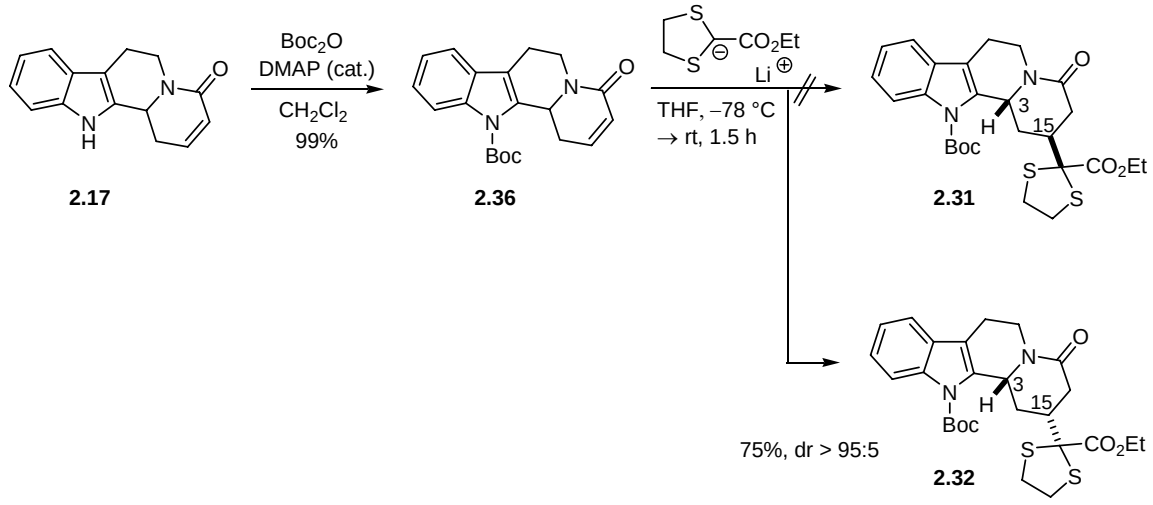
Scheme 2.21



2.13 UNEXPECTED REVERSAL OF DIASTEREOSELECTIVITY IN THE 1,4-ADDITION

During the optimization and streamlining phase of the project we decided to reinvestigate the idea of introducing an indole protecting group prior to the 1,4-addition in order to attempt the conjugate addition and the subsequent alkylation in the same pot. Toward this end Michael acceptor **2.12** was treated with Boc_2O and catalytic DMAP in THF to afford **2.36** in 99% yield. With an ample supply of Boc-protected Michael acceptor **2.36** in hand, we turned our attention to the key 1,4-addition. However; exposure of **2.36** to the lithium enolate of ethyl-1,3-dithiolane-2-carboxylate did not result in the formation of the expected Michael adduct **2.31**. Rather, its C(15) epimer **2.36** was isolated in 71% yield as a single diastereomer (Scheme 22).[81]

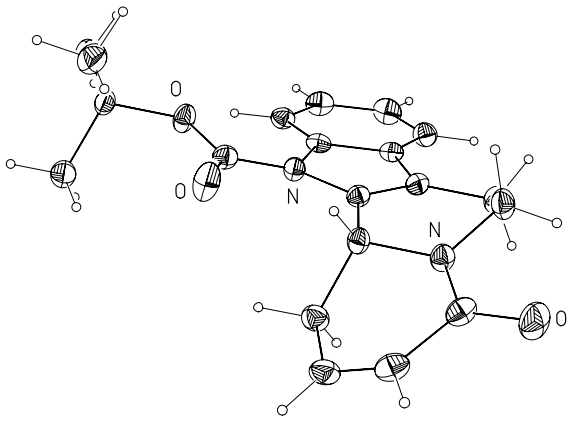
Scheme 2.22



In order to gain insight into the origin of this unexpected reversal in diastereoselectivity, a single crystal X-ray analysis was performed on Michael acceptor **2.36**. As shown in Figure 2.3, the α,β-unsaturated lactam moiety is twisted out of the plane defined by the indole and the Boc group. Operating under the assumption that the structure in solution bears a resemblance to that in the solid state, one can see that the top

face of the α,β-unsaturated lactam is no longer the more sterically accessible face because it is blocked by of the presence of the bulky Boc group. The incoming nucleophile is therefore redirected to the bottom face of the α,β-unsaturated lactam through steric approach control, which appears supersede the typical preference of axial attack. An alternative explanation may be that 1,4-addition occurs via axial attack on the opposite half-chair conformer of the α,β-lactam **2.36**, although the nucleophile would experience a 1,3-diaxial interaction in such a transition state.

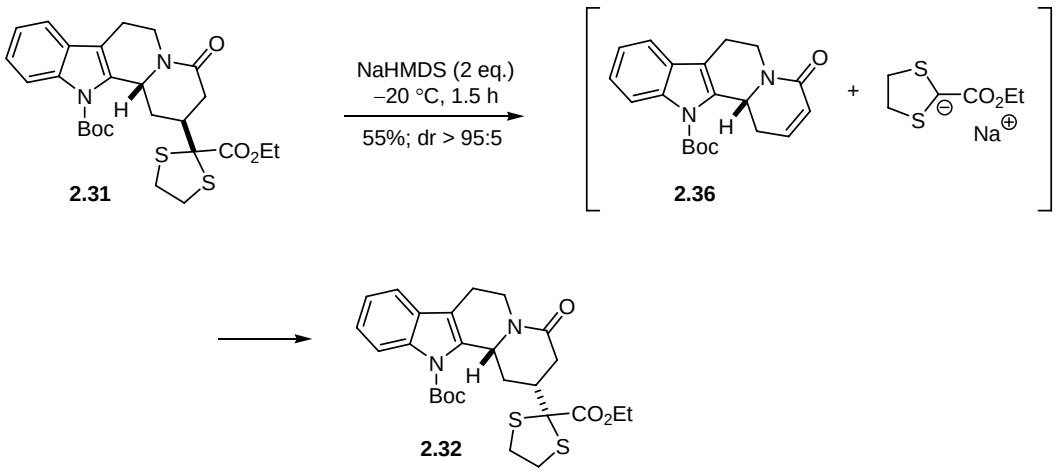
Figure 2.3 ORTEP plot of **2.36**. Displacement ellipsoids are scaled to the 50% probability level.



The interesting and unexpected reversal of diastereoselectivity in the 1,4-addition was corroborated during one of the numerous experiments aimed at optimizing the alkylation of lactam **2.31**. Because of the significant amounts of side products that were formed during the early alkylation studies, we decided to examine the stability of the enolate of **2.31**. In the event, **2.31** was deprotonated with NaHMDS at −78 ˚C and then incubated at −20 ˚C for 1.5 h, whereupon the reaction was cooled again to −78 ˚C and quenched (Scheme 2.23). Interestingly, the NMR spectrum of the crude reaction mixture did not show any of the notorious retro-Michael product **2.36** that was frequently

observed in the early alkylation experiments. Instead, the spectrum indicated the presence of the C(3)-H/C(15)-H *cis* diastereomer **2.32**, which was isolated in 55% yield after purification by chromatography. The formation of this diastereomer can be rationalized as resulting from retro-Michael reaction followed by 1,4-addition from the less sterically encumbered face of **2.36**, which is in accordance with the results shown in scheme 2.22.[81]

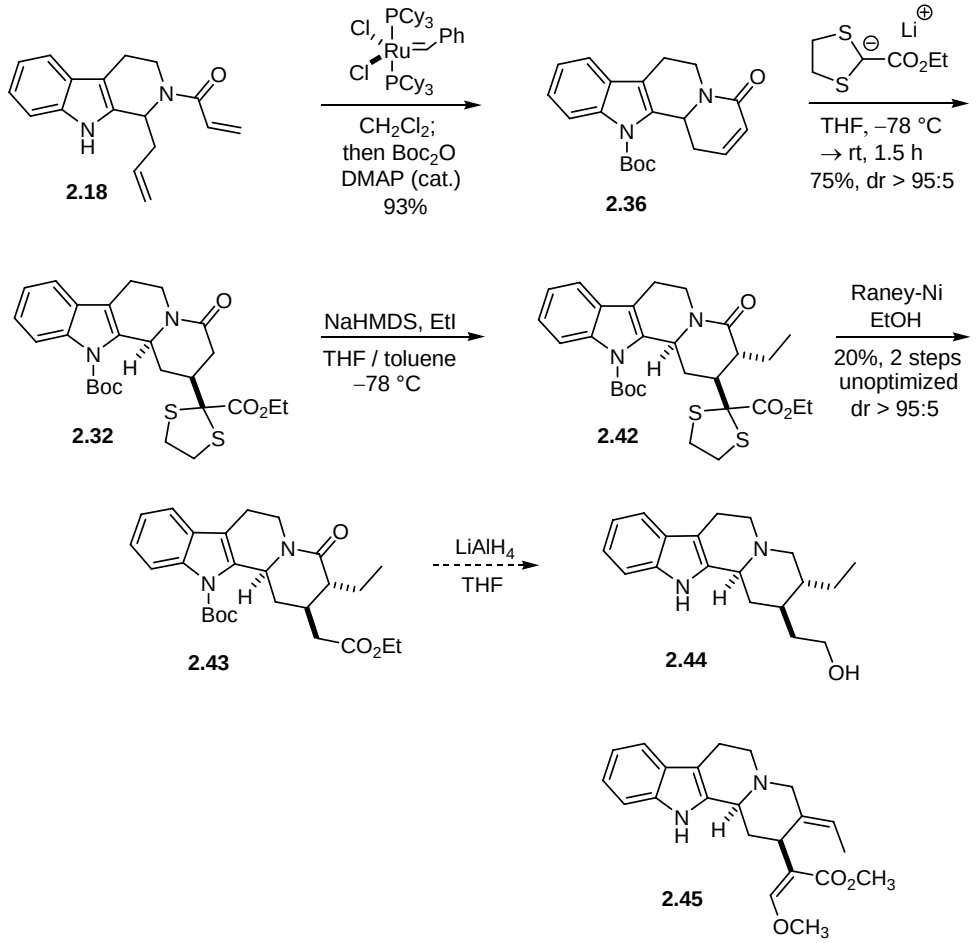
Scheme 2.23



2.14 SYNTHESIS OF THE CARBON SKELETON OF DIHYDROCORYNANTHEOL

The fact that the stereochemistry of the 1,4-addition can be efficiently controlled through steric approach control greatly expands the scope of the RCM/1,4-addition approach to corynanthe alkaloids. Simply though re-sequencing two of the steps in the synthesis, we now have the opportunity to access structures with either a C(3)-H/C(15)-H *trans* or a C(3)-H/C(15)-H *cis* stereochemical relationship, the latter of which is the configuration of the "normal" corynanthe alkaloids such as dihydrocorynantheol (**2.44**) and geissoschizine (**2.45**). To explore the scope of this approach, the total synthesis of dihydrocorynantheol was pursued (Scheme 2.24).

Scheme 2.24



It was possible to streamline the synthesis of the Boc protected Michael acceptor **2.36** by combining the ring-closing metathesis of acrylamide **2.18** with the subsequent protection step. By simply adding Boc_2O and catalytic DMAP upon completion of RCM reaction, the protected Michael acceptor **2.18** could be isolated in 93%, which is a slight improvement over the stepwise procedure (86% overall yield). Following 1,4-addition of the lithium enolate of ethyl-1,3-dithiolane-2-carboxylate to **2.18**, attempts to install the C(20) ethyl group in order to complete the construction of **2.44** were undertaken. Surprisingly, alkylation of the sodium enolate of **2.32** with ethyl triflate using the

optimized conditions for the alkylation of **2.31** resulted in an intractable reaction mixture. On the other hand, running the alkylation at −78 °C using the less reactive electrophile ethyl iodide, afforded the desired product **2.42** in 20% yield (unoptimized) along with 35% recovered starting material. The purification of **2.42** was complicated by the presence of side products that could not be completely removed by chromatography, and efforts to recrystallize **2.42** failed. Nevertheless, **2.42** was reduced with Raney Ni to afford **2.43**, which could be obtained cleanly in 18% yield over the two steps, thus completing the carbon skeleton of dihydrocorynantheol (**2.44**). It is not inherently clear why **2.32** should be more difficult to alkylate than its diastereomer **2.31**, and more experimentation would be needed to make this a viable route to dihydrocorynantheol. After optimization of the alkylation, one can envision the completion of the synthesis of **2.44** by simply refluxing **2.43** in the presence of $LiAlH_4$ to effect the necessary reductions to afford the natural product.

2.15 CONCLUSION

A unified approach to the synthesis of corynanthe and oxindole alkaloids that employs an RCM/1,4-addition strategy has been developed. This culminated in the formal syntheses of hirsutine, rhynchophylline, and the carbon skeleton of dihydrocorynantheol. The advantage of this strategy over the majority of previous approaches is that it allows access to both the normal and pseudo corynanthe alkaloids, which have a C(3)-H/C(15)-H *cis,* and C(3)-H/C(15)-H *trans* stereochemical relationship respectively. The syntheses diverge in a highly stereoselective manner from a common intermediate upon the efficient control of the stereochemistry in the 1,4-addition. This may facilitate the preparation of analogs of these biologically valuable alkaloids. The development and application of 1,4-additions to *unactivated* α,β-unsaturated lactams was

significant in that the majority of literature examples involve prior activation of the lactam by the incorporation of electron withdrawing groups. In another key step, conditions were developed to allow for a highly diastereoselective alkylation of an exceedingly hindered lactam, a transformation with little precedence in the literature.

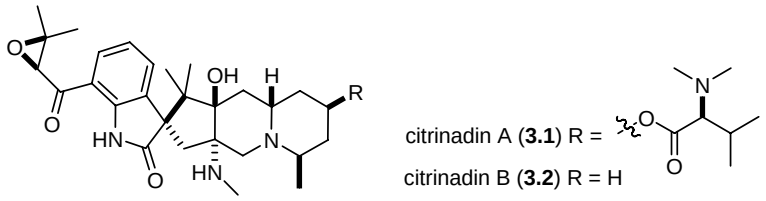
The synthesis of **2.4**, the formal target of hirsutine (**2.2**), proceeded in eight steps and 14.4% overall yield from **2.8** (10 steps from tryptamine). This compares favorably to Tietze's 11-step enantioselective synthesis of this intermediate. Among the diastereoselective racemic total syntheses of **2.2**, the syntheses of Wenkert, Brown, and Lounasmaa were shorter than our approach, but the overall yields were lower (less than 7.8%, 3.8%, and 1.1% respectively). Additionally, unlike our synthesis, none of these approaches are readily adapted to the enantioselective synthesis of **2.2**. The formal synthesis of rhynchophylline (**2.1**) proceeded in 11 steps and 5.4% overall yield to *epi*-**2.3** (13 steps from tryptamine). Although Ban's synthesis of **2.1** required only nine steps, it involved four separations of diastereomers formed in almost equimolar ratios due to early formation of the configurationally labile oxindole skeleton and a non-selective introduction of the C(20) ethyl group.

Chapter 3: Citrinadin A and B: Syntheses of Spirooxindoles

3.1 INTRODUCTION

Marine-derived fungi represent an important source of structurally diverse secondary metabolites that often possess significant biological activity.[82] In the fall of 2004, Kobayashi and co-workers reported the isolation and structure elucidation of citrinadin A (**3.1**), a novel pentacyclic spiroindolinone alkaloid.[83] This marine natural product was obtained from the fermentation broth of the fungus *Penicillium citrinum* (strain N-059), derived from the red alga *Actinotrichia fragailis*, which was collected at Hedo Cape, Okinawa Island. Citrinadin A (**3.1**) features a densely functionalized carbon skeleton including nine stereogenic centers, an α,β-epoxy carbonyl moiety, and a rare *N*,*N*-dimethylaminovaline residue. The latter functional group has only been observed in two other natural products: 14-(*N*,*N*-dimethyl-L-valyloxy)paspaline, obtained from a fungus,[84] and the dolastatins, which were isolated from sea hares.[85] In 2005, Kobayashi also reported the isolation of the closely related analogue citrinadin B (**3.2**), which differs from (**3.1**) only in that it lacks the hydroxyl substituent on the piperidine ring.[86]

Figure 3.1



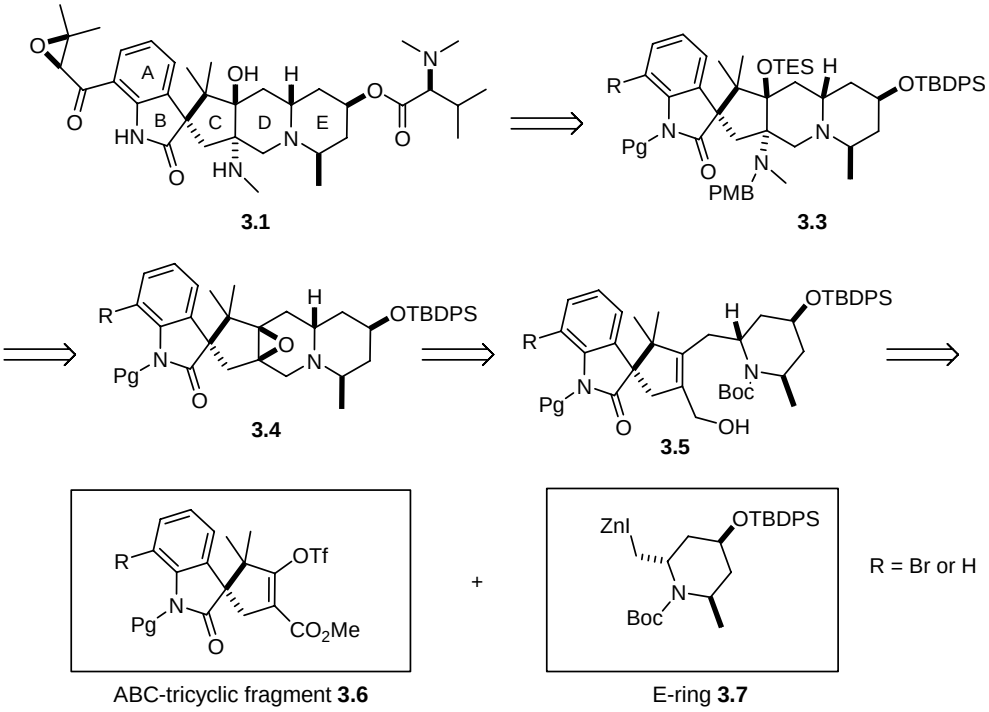
Over the years a number of spiroindolinone alkaloids have been isolated from fungi of the *Penicillium* or *Aspergillus* genera including the brevianamides,[87]

paraherquamides,[88] marcfortines,[89] and sclerotamide.[90] Although these alkaloids contain structural similarities to **3.1** and **3.2**, the molecular architecture and substitution pattern displayed by citrinadin A and B are unique. Furthermore, preliminary biological assays demonstrated that **3.1** exhibits cytotoxicity against murine leukemia L1210 (IC_{50} = 6.2 μg/mL) as well as human epidermoid carcinoma KB cells (IC_{50} = 10 μg/mL)[83] making it an attractive target for total synthesis. To date, no total synthesis or synthetic studies have been reported of citrinadin A or B. We anticipated that the pursuit of the enantioselective total synthesis of **3.1** would likely inspire the development of potentially useful and general solutions to a variety of synthetic problems (*vide infra*).

3.2 RETROSYNTHETIC ANALYSIS/SYNTHETIC CHALLENGES

It was envisioned that the natural product **3.1** could be derived from the late-stage intermediate **3.3** via a directed *ortho*-metallation of the indole and trapping as a stannane, which in turn could undergo palladium mediated cross-coupling with an appropriately functionalized acid chloride to install the α,β-epoxy carbonyl moiety (Scheme 3.1). While *ortho*-metallation of indoles have been demonstrated,[91a] there is no precedent for the corresponding reaction of oxindoles. If such a process cannot be realized it may be necessary to incorporate a halogen in the indole 7-position from the start of the synthesis. In that case, several options exist for the introduction of the α,β-epoxy carbonyl moiety. The most direct approach would involve using a mild protocol developed by Gosmini, in which the aryl bromide is converted to an aryl zinc species that readily undergoes cross-coupling with acid chlorides.[92]

Scheme 3.1

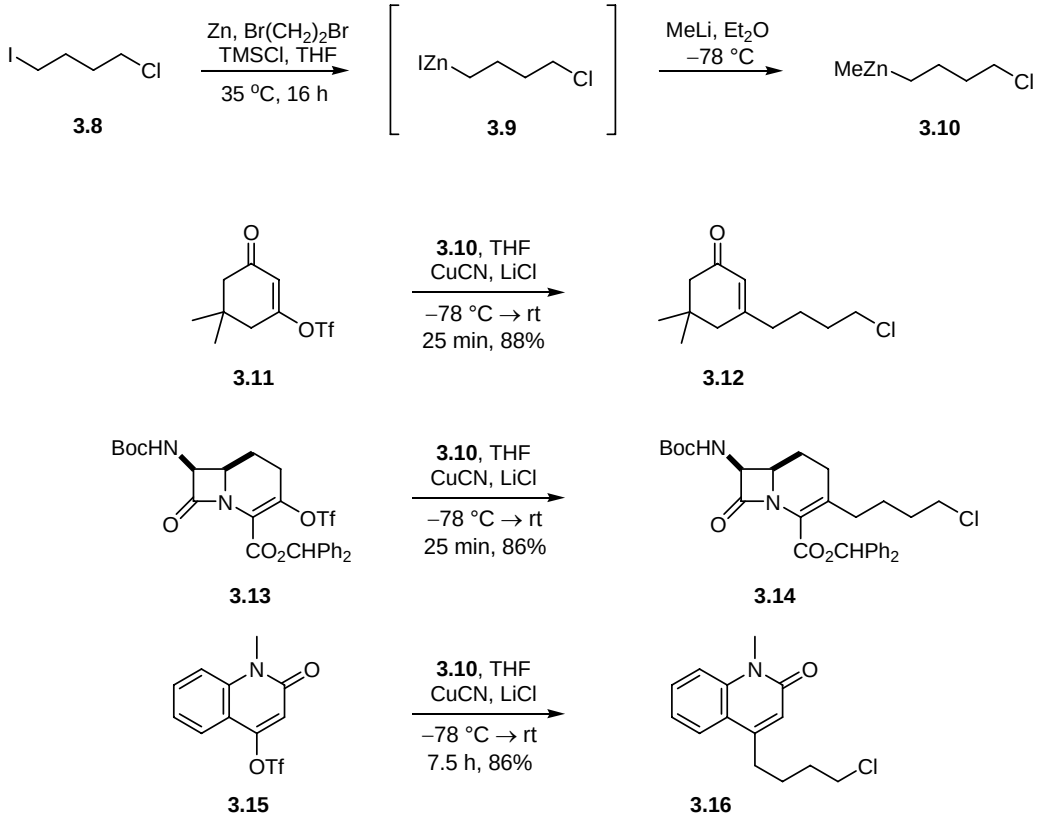


The *N,N*-dimethylaminovaline residue will be installed on the quinolizidine section of the molecule via EDCI-mediated esterification of a secondary alcohol. Late stage intermediate **3.3** may be obtained from **3.4** through the addition of a methylamine-derived nucleophile via *trans*-diaxial opening of an epoxide at the less hindered carbon. Although we recognized that this may be a significant synthetic challenge, this transformation has been demonstrated in hindered systems using amino-magnesium species as nucleophiles.[93] Pentacyclic intermediate **3.4**, in turn, would be obtained from tetracycle **3.5** via Sharpless asymmetric epoxidation according to close literature precedent,[94] followed by D-ring formation via intramolecular alkylation.

The tetracycle **3.5** was projected to arise from addition/elimination of the Knochel cuprate of alkyl zinc species **3.7** to the alkenyl triflate **3.6** following chemistry described by Lipshutz.[95] In this method, Lipshutz converted alkyl halides such as **3.8** to the

corresponding alkyl zinc halides **3.9** by direct insertion of zinc that had been activated with TMSCl and dibromoethane (Scheme 3.2).[96] Since alkyl zinc halides are fairly unreactive, methyllithium was added to generate the more reactive dialkyl zinc species **3.10**, in which the methyl group serves as a nontransferable ligand. This species underwent facile addition/elimination to a variety of substrates in the presence of 3 mol % CuCN·LiCl (Scheme 3.2).

Scheme 3.2

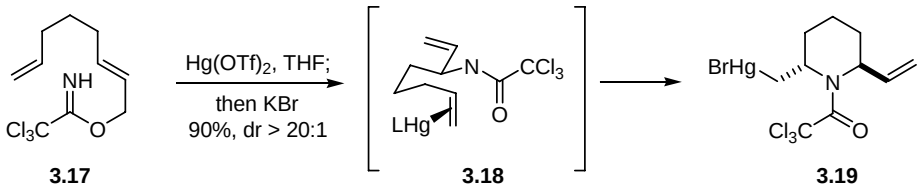


The application of this tactic to the fragment coupling of **3.6** and **3.7** would result in a highly convergent synthesis, but would also entail significant challenges because of the steric hindrance of triflate **3.6**. Not only is the triflate neopentyl but it is also flanked on both sides by the spirooxindole unit. Furthermore, all examples by Lipchutz and co-

workers utilized linear nucleophiles whereas the proposed fragment coupling would entail the use of the β-branched alkyl zinc species **3.7**. As such, this provided an opportunity to examine and potentially expand the scope of this useful coupling methodology.

In preparation for the fragment coupling, an efficient enantioselective synthesis of the trisubstituted piperidine **3.7** will be required. Although numerous methods have been described for the synthesis of piperidines with various substitution patterns, there are not as many general methods available for the synthesis of *trans*-2,6-dialkyl piperidines as there are for *cis*-2,6-disubstituted piperidines.[97] Singh and Han have recently described a facile entry into these systems, which utilizes a tandem Overman rearrangement/mercury cyclization (Scheme 3.3).[98] The high *trans* selectivity in the mercury cyclization was attributed to steric repulsion between the *N*-trichloroacetyl group and the mercury complexed terminal olefin in **3.18**. Since organomercurials can be directly converted to alkyl iodides,[99] the application of this mercury cyclization could potentially allow for a rapid synthesis of the iodide precursor to **3.7**. However, it would require the enantioselective synthesis of a suitable substrate related to **3.18** incorporating an oxygen substituent in the 4-position, which in turn may influence the stereoselectivity of the mercury cylization. Another possibility would be to carry out the cyclization using iodine to afford the requisite iodide directly.[100]

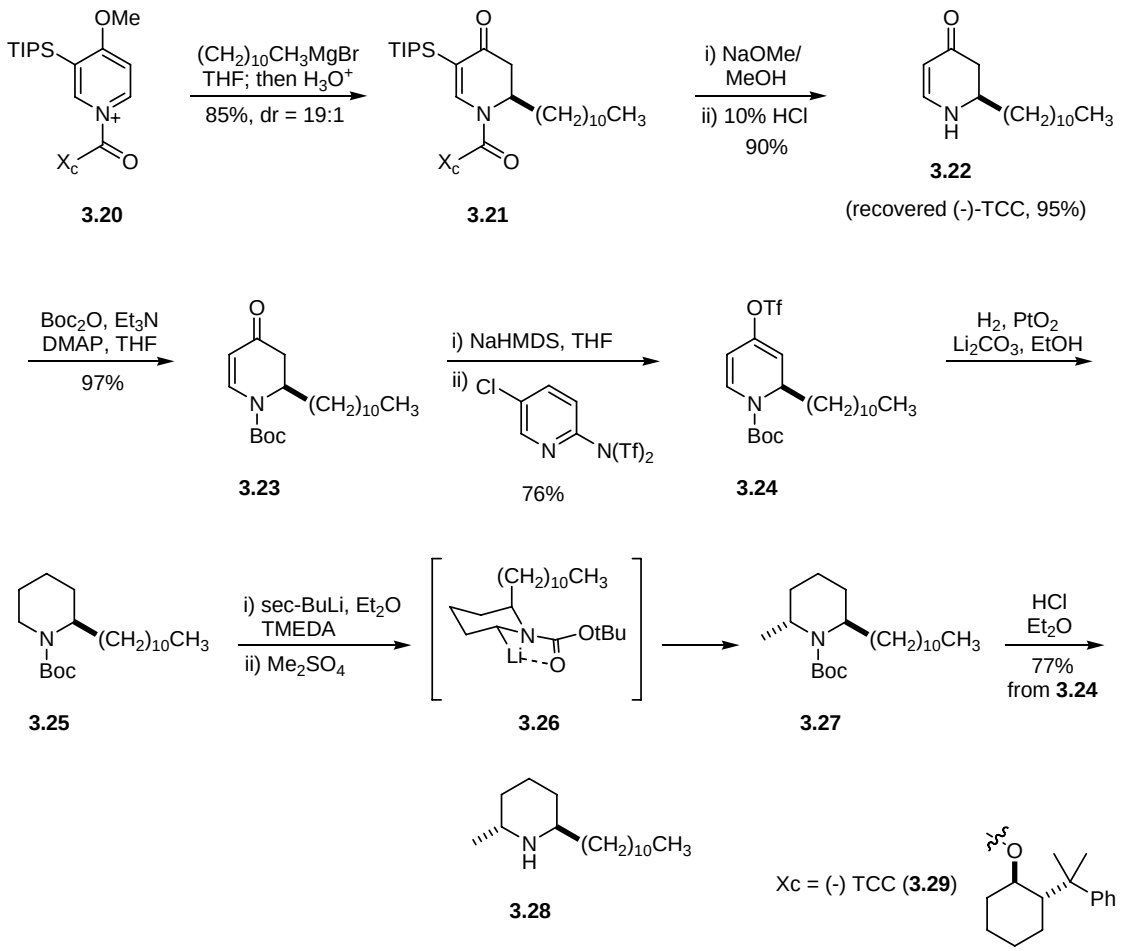
Scheme 3.3



3.17 **3.18** **3.19**

A more straightforward, albeit somewhat longer, approach may involve the application of methodology developed by Comins[101] coupled with a *trans*-selective Beak lithiation.[102] Comins and co-workers have demonstrated that acyl pyridinium salts such as **3.20**, derived from 4-methoxy-3-(triisopropyl)pyridine and the chloroformate of (-)-*trans*-2-(α-cumyl)cyclohexanol ((-)-TCC), undergo addition of Grignard reagents in good yield and high diastereoselectivity. The presence of the TIPS group was necessary to ensure high diastereoselectivity. This methodology has been applied to the enantioselective synthesis of a number of natural products including Solenopsin A (**3.28**)[101,103] (Scheme 3.4).

Scheme 3.4



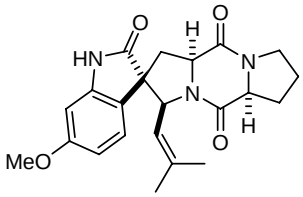
A convenient one-pot procedure involving the exposure of **3.21** to NaOMe/MeOH followed by 10% HCl delivered **3.22** where both the TIPS group and the TCC auxiliary had been removed. The auxiliary could be recovered in 95% yield at this point. Following elaboration of **3.22** to **3.25**, the stage was set for the *ortho*-directed lithiation to introduce the requisite methyl group and establish the 2,6-*trans* stereochemical relationship. This reaction, which was developed by Beak and co-workers, relies on the directing effect of the Boc protecting group.[102] The substituent in the 2-position is axially disposed in order to minimize $A^{1,3}$ strain resulting from the partial double bond character of the amide

bond. With the equilibrium favoring this chair conformation, the carbonyl oxygen of the Boc group directs deprotonation of an equatorial proton. The resultant lithiated species **3.26** undergoes alkylation with retention of configuration to deliver the *trans*-2,6-dialkyl species **3.27** in excellent yield and diastereoselectivity.

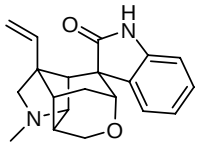
3.3 SYNTHESES OF SPIROOXINDOLES

One of the major challenges in the proposed synthesis of citrinadin A will be the enantioselective synthesis of the ABC-tricyclic fragment **3.6**. Its densely functionalized carbon skeleton contains a five membered ring bearing two adjacent quaternary centers, one of which is a stereogenic center in addition to being spirocyclic. There are a plethora of methods available in the literature for the synthesis of spiro[pyrrolidine-3,3'-oxindoles], that contain a nitrogen in the five membered ring as exemplified by spirotryprostatin (**3.30**) (Figure 3.2).[104] On the contrary, not as many general methods have been devised for the enantio- or stereoselective construction of spirooxindoles composed of an all-carbon frame work as in citrinadin A. Gelsemine (**3.31**) represents another structurally intriguing alkaloid that has generated considerable interest in the synthetic community, and its challenging spirooxindole motif has inspired the development of several new methods for its efficient construction. The remainder of this chapter will focus on the various approaches the spirooxindole of gelsemine and other natural products, along with recent methodology development.

Figure 3.2



spirotryprostatin (**3.30**)



gelsemine (**3.31**)

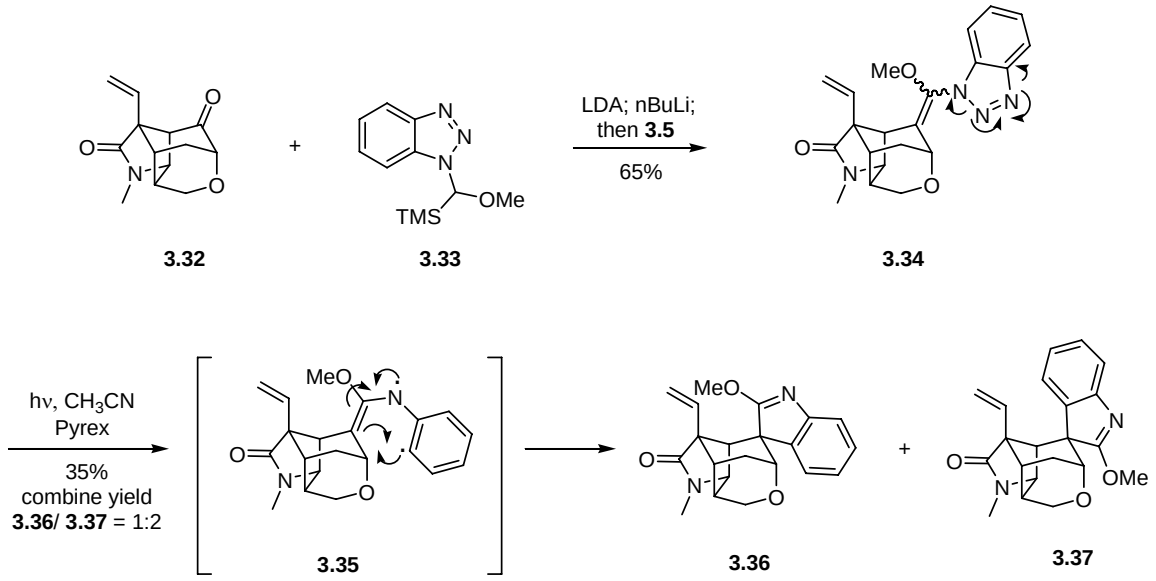
3.3.1 Spiroannelation via Photoinduced Formation of a Diradical Species

Gelsemine (**3.31**) has served as a testing ground for new methodology for the synthesis of spirooxindoles. In Johnson's 1994 approach to this challenging alkaloid, a method for the conversion of ketone **3.32** to a spirooxindole was required.[105] It was quickly determined, however, that the steric congestion of this ketone precluded the use of many of the conventional methods for constructing quaternary centers.[106] A solution to this problem was eventually devised that involved a photochemical reaction to generate a diradical that could undergo ring closure. As depicted in Scheme 3.5, the benzotriazole derivative **3.33** was lithiated and then condensed with ketone **3.32** via a Peterson-type olefination. The product **3.34** was obtained as a mixture of *E*/*Z* isomers, which were separated and subjected independently to the ensuing photochemical transformation. In the event, irradiation of **3.34** resulted in the fragmentation of the benzotriazole to expel nitrogen and generate a diradical **3.35**, which could recombine to give the diastereomeric spiro-derivatives **3.36** and **3.37** in a 1:2 ratio. The requisite spirooxindoles could then be formed through acid hydrolysis.

In spite of the low yield and the poor diastereoselectivity favoring the unwanted diastereomer, Johnson's success in converting the sterically encumbered ketone **3.32** to the requisite spirooxindole was a notable achievement. Flemming had previously attempted to convert a ketone similar to **3.5** and developed three spirooxindole syntheses,

none of which actually worked in the real system.[107] Nevertheless, Johnson's work illustrates the challenge of constructing this type of spirooxindole in good yield and diastereoselectivity. As a consequence, this problem became the focus of a number of synthetic groups during the ensuing decade. Since the proposed route to citrinadin A (Scheme 3.1) requires the enantioselective preparation of the spirocyclic fragment **3.6**, Johnson's strategy may not be applicable since it does not address the issue of absolute stereochemistry.

Scheme 3.5



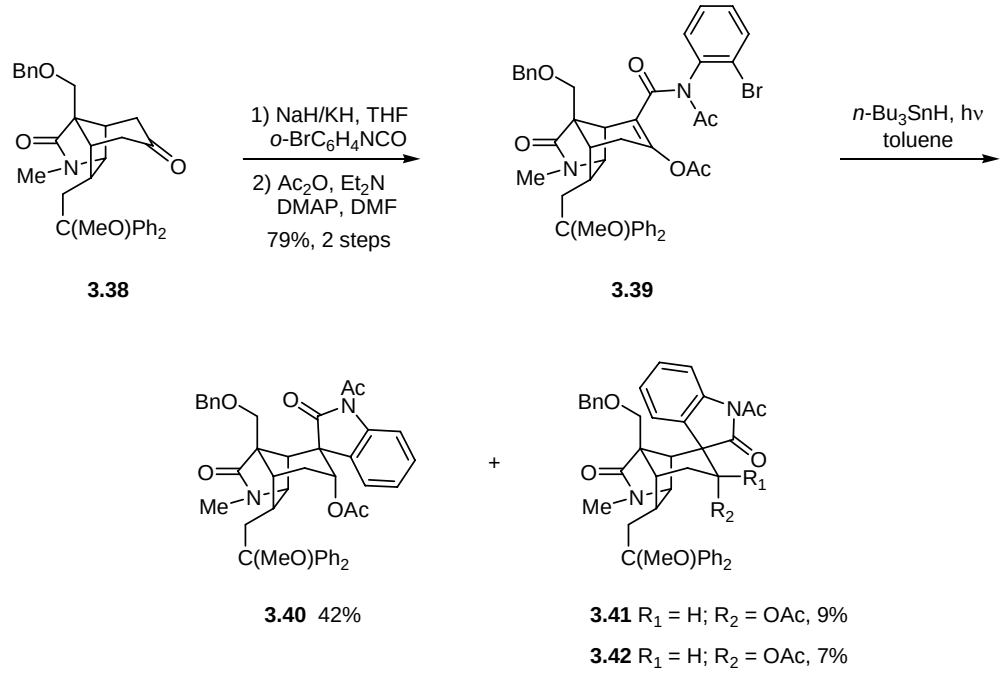
3.3.2 Spirooxindoles via Radical Cyclization

Radical cyclization represents a fairly general method for the construction of spirooxindoles, and this tactic was employed by Hart and co-workers in their total synthesis of gelsemine (Scheme 3.6).[108] These workers discovered that excellent regiochemistry could be attained during the enolization of ketone **3.38**. As a result, the *o*-bromoanilide moiety could be efficiently incorporated through acylation using *o*-

bromophenyl isocyante as the acylating agent. Following conversion to **3.39**, the stage was set for the key radical cyclization. In the event, irradiating a solution of **3.39** and *n*-Bu_3SnH in refluxing toluene afforded the desired spirooxindole **3.40** in 42% yield, along with the two unwanted diastereomers **3.41** and **3.42** in 9% and 7%yields respectively. One should note that considerable effort was required to identify **3.39** as the optimal substrate for this key transformation, as the cyclization using substrates with different protecting groups suffered from poor yields and/or low diastereoselectivity.

Radical cyclization represents a potentially useful method for the construction of such challenging spirocyclic motifs as the one present in gelsemine. Furthermore, Jones[109] and Murphy[110] have recently demonstrated the utility of radical cyclizations in the synthesis of spiro[pyrrolidine-3,3'-oxindoles]. However, as in the case of Johnson's photo induced transformation (*vide supra*), this method does not address the absolute stereochemistry. Additionally, the low yield and diastereoselectivity would limit its utility in the synthesis of citrinadin A

Scheme 3.6

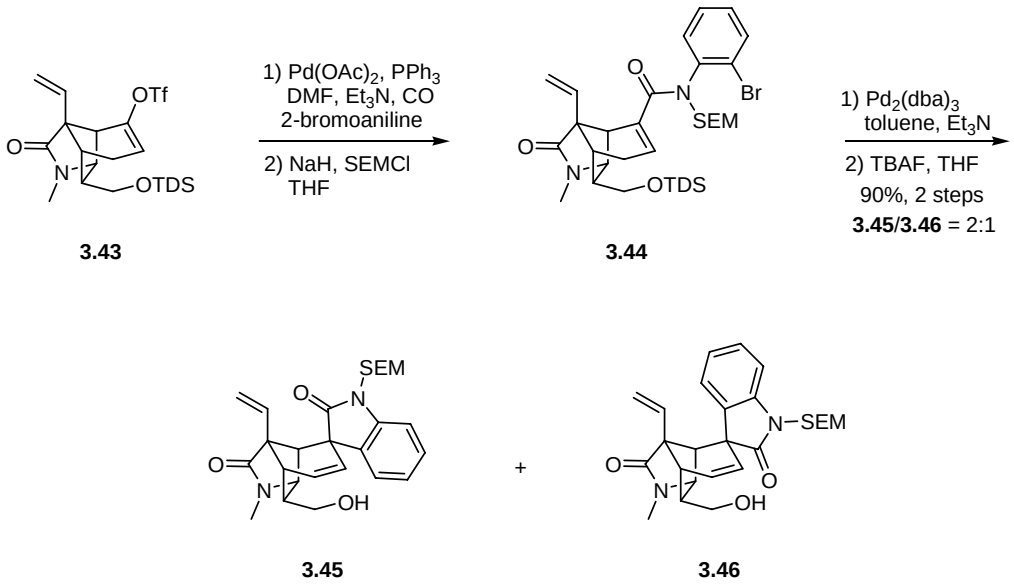


3.3.3 Spirooxindoles via Intramolecular Heck Reaction

In 1987 Overman and co-workers demonstrated the application of an intramolecular Heck reaction to the construction of spirooxindoles.[111] The utility of this transformation did not go unnoticed by the synthetic community, and in 1994 Hiemstra and Speckamp applied an intramolecular Heck reaction in their total synthesis of gelsemine.[112] The synthesis of the spirooxindole unit starting from triflate **3.43**, which was subjected to a carbonylation reaction to deliver anilide **3.44**, following protection of the amide nitrogen with a SEM group (Scheme 3.7). This material then served as the substrate for the key spiroannulation reaction. In the event, exposure of **3.44** to $Pd_2(dba)_3$ and Et_3N in toluene at room temperature for 4 h delivered spirooxindoles **3.45** and **3.46** in 90% yield and a 2:1 diastereomeric ratio in favor of the desired spirooxindole **3.45**. This successful application of an intramolecular Heck reaction to the synthesis of the

exceedingly hindered spirooxindole of gelsemine serves as a powerful testimony to the utility of this transformation.

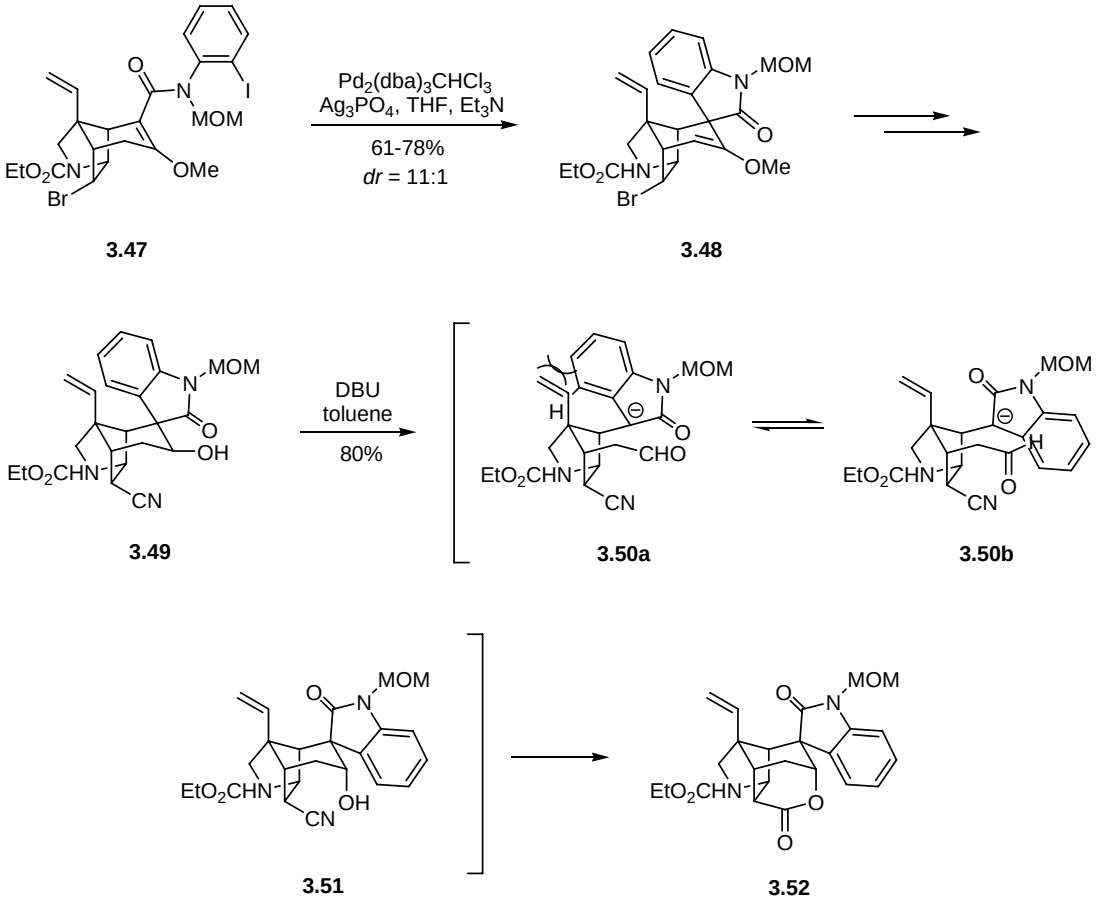
Scheme 3.7



A few years following Speckamp's synthesis of gelsemine, Overman and co-workers reported their approach.[113] The intramolecular Heck reaction was again featured as the key step in constructing the spirooxindole unit, but their system was slightly different than the one employed by the Speckamp group. Because in Overman's synthesis, a vinylogous carbamate **3.47** was used, a migratory insertion of an aryl palladium species into a tetrasubstituted olefin would be required (Scheme 3.8). Nevertheless, the reaction proceeded in 61-78% yield to deliver spirooxindole **3.48** in a diastereomeric ratio of 11:1. Unfortunately, the major isomer was in fact the undesired diastereomer, and it was therefore necessary to epimerize the spiro-center. Following elaboration of **3.48** to **3.49**, this goal was achieved by refluxing **3.49** in toluene in the presence of DBU to effect a major skeletal reorganization. This transformation was

presumed to occur via initial retro-aldol reaction to give **3.50a**. In order to minimize steric repulsion between the oxindole aryl ring and the vinyl group this material undergoes C-C bond rotation to give **3.50b**, whereupon ring-closure can occur via an aldol reaction. The latter transformation was followed by addition of the resultant axial hydroxyl group in **3.51** to the nitrile to form the final ring and deliver **2.52** in 80% yield. Again, the intramolecular Heck reaction has proved to be useful in constructing sterically hindered spirooxindole units. One remaining limitation, however, is the problem of diastereoselectivity as seen in both Johnson's and the Overman's syntheses of gelsemine.

Scheme 3.8

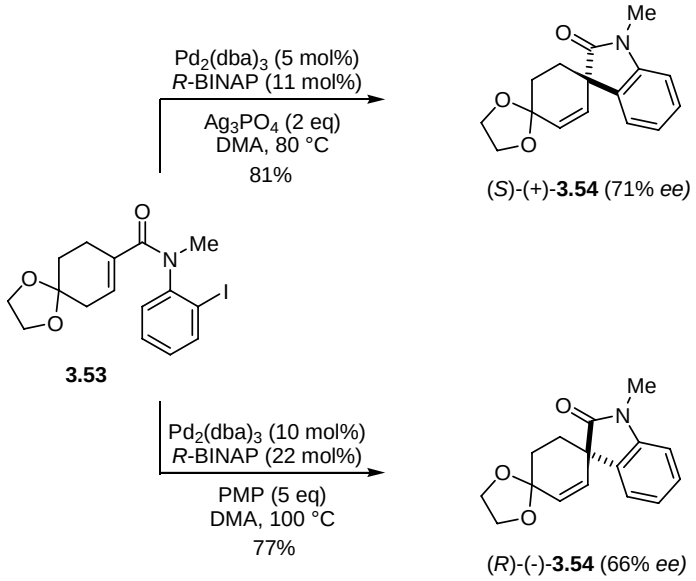


3.3.4 Spirooxindoles via the Asymmetric Intramolecular Heck Reaction

The asymmetric version of the intramolecular Heck reaction was discovered and reported independently by Shibasaki and Overman in 1989.[114] Overman and co-workers applied this transformation to the asymmetric synthesis of spirooxindoles, and they were able to obtain moderate levels of enantioselectivity as shown in Scheme 3.0.[115] Surprisingly, either enantiomer of the spirooxindole **3.54** could be obtained using the same enantiomer of the chiral diphosphine ligand depending on whether Ag_3PO_4 or PMP was used as the HI scavenger. While the asymmetric Heck reaction has proven extremely

powerful in the synthesis of a number of indole and oxindole alkaloids, it is unclear, whether or not this transformation could be applied to the synthesis of citrinadin A. A potential problem would be the presence of the gem-dimethyl substituents, which would incur unfavorable steric interactions with the aryl palladium species in the transition state. The moderate levels of enantioselectivity represent an additional limitation to this methodology

Scheme 3.9

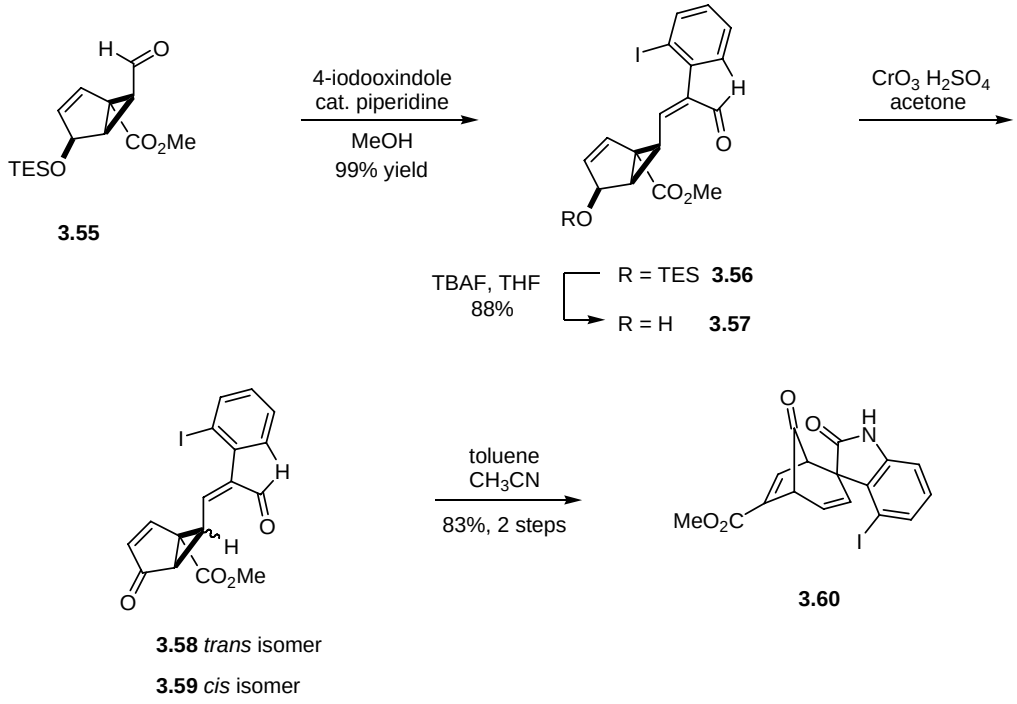


3.3.5 Spirooxindoles via Divinylcyclopropane Rearrangement

A major drawback with all the previous approaches to the gelsemine spirooxindole unit was the lack of control over stereochemistry. To address this problem Fukuyama and co-workers developed an efficient strategy using a divinylcyclopropane rearrangement as a key step that allowed for the incorporation of the spirooxindole with complete diastereoselectivity.[116] The substrate for the key step was prepared through a Knovenagel condensation of aldehyde **3.55** with 4-iodooxindole to give **3.56** in excellent

yield as a single olefin regioisomer (Scheme 3.10). During the development of the racemic synthesis of gelsemine using a system closely related to **3.55**, it was discovered that the use of a substituted oxindole bearing a bulky iodide in the 4-position was crucial in order to obtain good *E*/*Z*-selectivity in the Knovenagel condensation. In fact, performing this condensation using oxindole itself resulted in a mixture (4:1) of *E*- and *Z*-isomers. Following deprotection of the silyl group, the resultant secondary alcohol **3.57** underwent Jones' oxidation to give a mixture of cyclopropane *cis* and *trans* isomers **3.58** and **3.59**. This was of no concern since both isomers underwent the key rearrangement equally well. Thus, heating the mixture to 80 °C in toluene/acetonitrile induced the key divinylcylopropane-cycloheptadiene rearrangement to afford **3.60** in 83% yield over two steps.

Scheme 3.10

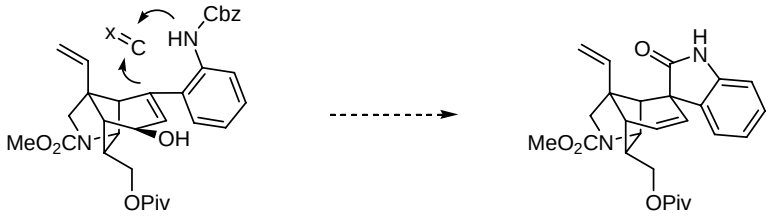


Fukuyama's approach to the spirooxindole of gelsemine represented an elegant solution to the challenging problem of controlling diastereoselectivity. On the other hand, the strategy is highly specific to the gelsemine ring-system, and could not be readily applied to the synthesis of the spirooxindole of citrinadin A.

3.3.6 Spirooxindoles via Eschenmoser Claisen Rearrangement

Danishefsky and co-workers envisioned the formation of spirooxindole **3.62** from allylic alcohol **3.61** via the incorporation of a one carbon unit (Scheme 3.11).[117] Unfortunately, all attempts to realize this goal using a [2.3] Still-Wittig or a Büchi rearrangement of allylic alcohol **2.61** were unsuccessful. The researchers were therefore forced to consider [3,3]-sigmatropic rearrangements as an alternative, although such a process would have the obvious disadvantage that it would generate a six membered ring that would require the excision of one carbon atom.

Scheme 3.11

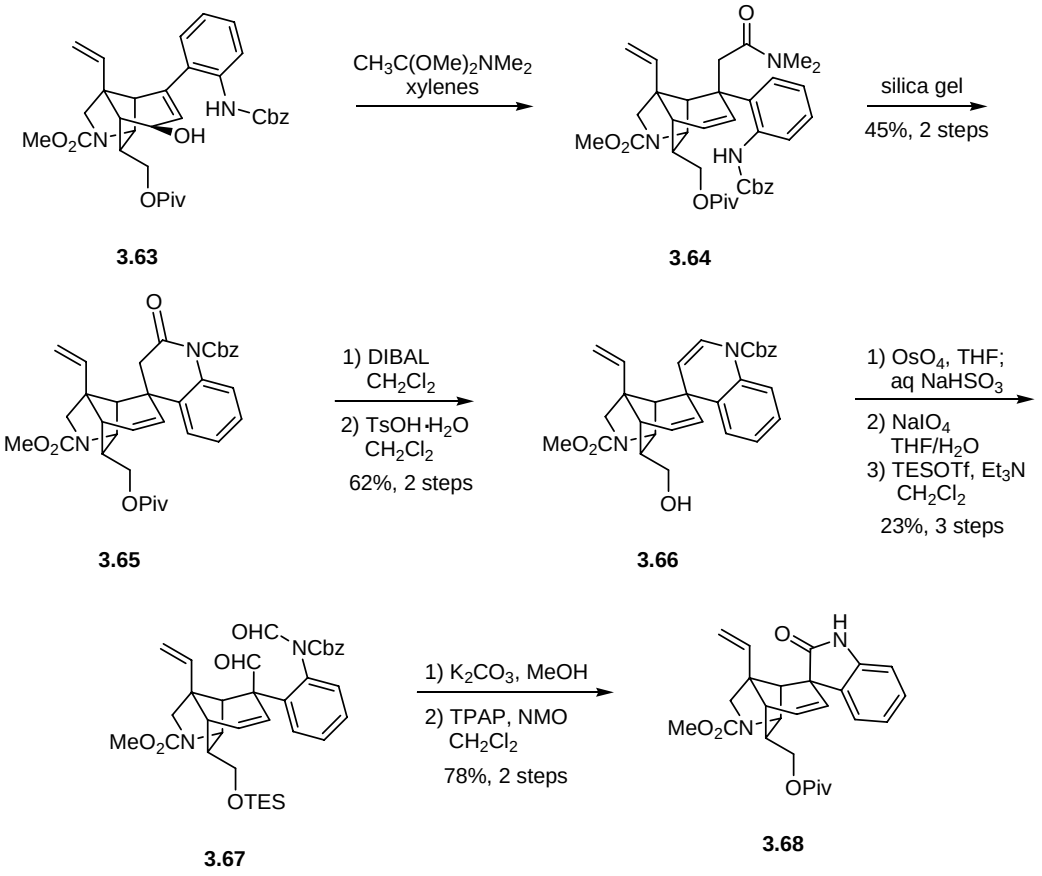


3.61 **3.62**

After much experimentation, the strategy involving a [3,3]-process was reduced to practice by a successful Eschenmoser amideacetal, Claisen rearrangement of **3.63** to afford **3.65** in 44% yield after exposure of intermediate **3.64** to silica gel (Scheme 3.12). Contraction of the six-membered spiro lactam commenced with the reduction of the lactam carbonyl followed by dehydration to give enamide **3.66**. Osmylation of the more electron rich olefin followed by periodate cleavage and silyl protection of the primary

hydroxyl group delivered **3.67** in moderate yield. Bis-aldehyde **3.67** was then subjected to K_2CO_3 in methanol resulting in the cleavage of the *N*-formyl group and spontaneous cyclization of the carbamate nitrogen with axial aldehyde to afford an aminal, oxidation of which furnished the requisite spirooxindole **3.68**. While the approach was eventually successful, the low yield of the rearrangement of **3.63** to **3.65** coupled with the need for a seven-step ring contraction would not allow for an efficient synthesis of the spirooxindole fragment of citrinadin A using this strategy.

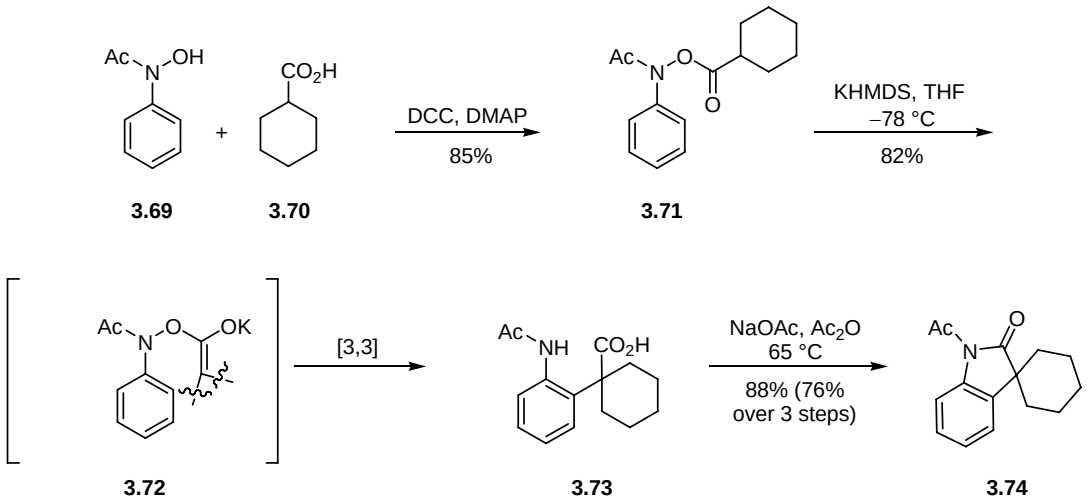
Scheme 3.12



3.3.7 Spirooxindoles via Hetero Claisen Rearrangement

Another example of [3,3]-sigmatropic rearrangements in the synthesis of spirooxindoles was reported by Baldwin and co-workers.[118] These researchers developed a three-step protocol, which is conceptually related to the Brunner oxindole synthesis,[119] and starts from a carboxylic acid using an Eschenmoser-Claisen reaction to construct the quaternary center. As depicted in Scheme 3.13, hydroxamic acid **3.69** underwent a DCC-mediated coupling with cyclohexane carboxylic acid (**3.70**). The corresponding product was treated with KHMDS at −78 °C to generate enolate **3.72**, which upon warming to room temperature underwent a [3,3]-sigmatropic rearrangement to give spiro-derivative **3.73**. Exposure of **3.73** to NaOAc and Ac_2O then effected the ring closure to furnish spirooxindole **3.74** in 75% yield over the three steps. It is notable that all the reactions proceeded very cleanly, and purification of the intermediates was not necessary.

Scheme 3.13

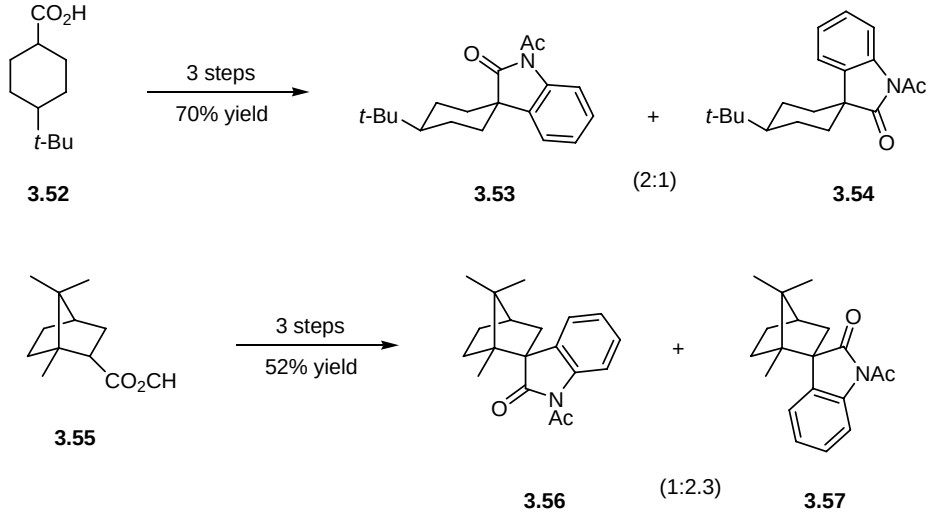


3.69 **3.70** **3.71** **3.72** **3.73** **3.74**

Baldwin and co-workers then sought to examine the stereochemical implications of their spiroannelation protocol (Scheme 3.14). A significant finding was that the procedure works well even in exceedingly hindered systems such as camphor carboxylic

acid (**3.78**), which underwent the three step sequence to give **3.79** and **3.80** in 52% overall yield. The diastereomeric ratio, however, was quite low affording the spirooxindoles **3.79** and **3.80** in a 2.3:1 dr. Because the diastereomeric ratios ranged from 1.6:1 to 2.8:1 this methodology is clearly limited. Nevertheless, Baldwin's oxindole synthesis represents a potentially useful approach that warrants further examination in the context of natural product synthesis.

Scheme 3.14

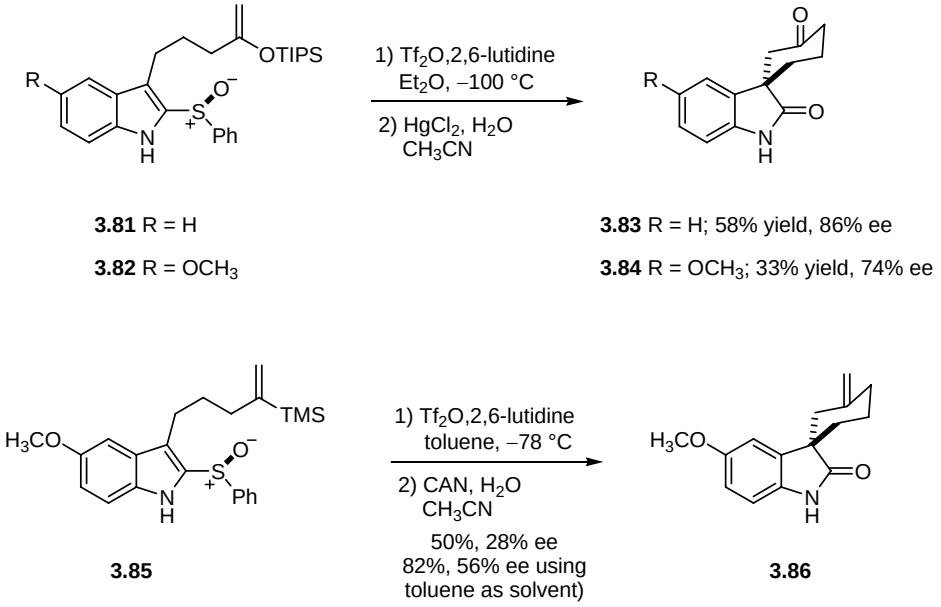


3.3.8 Spirooxindoles via Pummerer Reaction

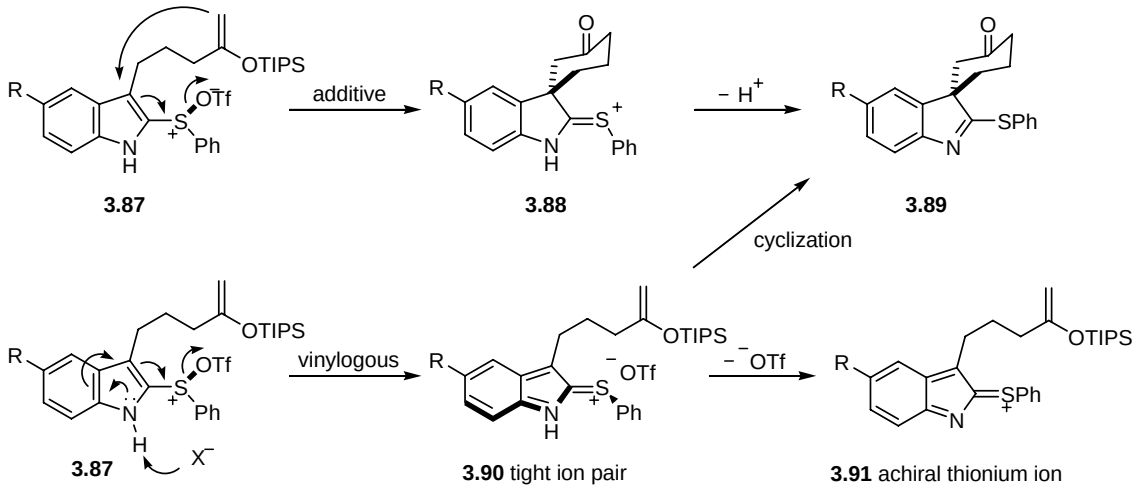
Feldman recently reported an interesting asymmetric spirooxindole synthesis involving a Pummerer reaction of chiral indole-2-sulfoxides bearing a nucleophile tethered to the 3-position of the indole (Sheme 3.15).[120] The reaction is of considerable mechanistic interest since it can be thought of as proceeding through two different pathways; additive or vinylogous (Scheme 3.16). Upon addition of triflic anhydride the resultant intermediate **3.87** can undergo direct cyclization of the tethered nucleophile onto the indole 3-position via a S_N2' mechanism (additive pathway). Alternatively, **3.87** can

ionize through the participation of the indole nitrogen lone pair (vinylogous pathway) to generate a tight ion pair **3.90,** that can either cyclize to afford the enantioenriched spirooxindole **3.89** or dissociate to furnish an achiral thionium species **3.91**.

Scheme 3.15



Scheme 3.16

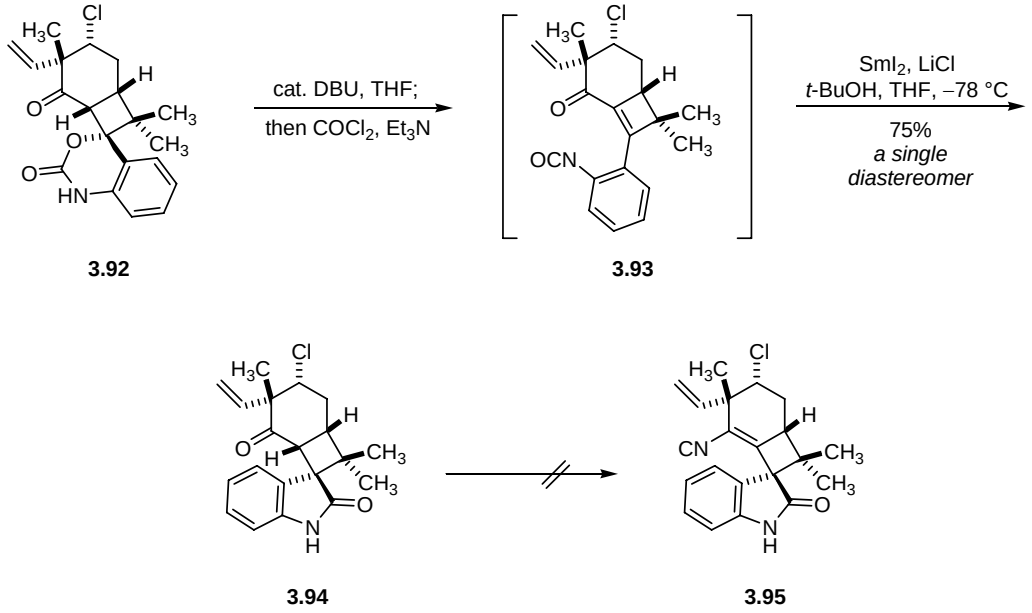


In order to achieve good chirality transfer, it was necessary to find conditions that would suppress the formation of the achiral thionium ion **3.91**. Scheme 3.15 shows the three examples that gave the highest ee's of the final oxindoles. The reactivity of the nucleophile was found to be important. Reactions with substrates bearing a silylenol ether such as **3.81** and **3.82** generally proceeded in higher ee than the less reactive vinylsilane **3.85** under identical conditions. Given the requirement that the cyclization event be fast in order to attain good yield and ee, this process may not be applicable to the synthesis of challenging spirooxindoles such as the one found in citrinadin A because of the presence of the gem-dimethyl substituent, which would require an S_N2'-like attack onto a neopentyl carbon.

3.3.9 Spirooxindoles via Nucleophilic Addition to an Aryl isocyanate

In the pursuit of the synthesis of (±)-welwitindolinone A (**3.95**), Wood and co-workers required a mild method for the diastereoselective formation of a spirooxindole in the presence of a sensitive cyclobutene ring.[121] Toward this end, Wood developed an attractive samarium diiodide mediated cyclization of an enone with an aryl isocyanate (Scheme 3.17). Isocyanate **3.93** was generated through the β-elimination of ketone **3.92** with DBU followed by loss of CO_2. The resultant aniline was then exposed to phosgene to generate the unstable isocyanate **3.93**, which following filtration to remove the HCl salts, underwent a reductive cyclization upon exposure to a solution of SmI_2/LiCl. The requisite spirooxindole **3.94** could be isolated in a 75% yield a single diastereomer. Unfortunately, the ketone of **3.94** was too sterically encumbered to be converted to the vinyl isonitrile that is present in the natural product **3.95**.

Scheme 3.17



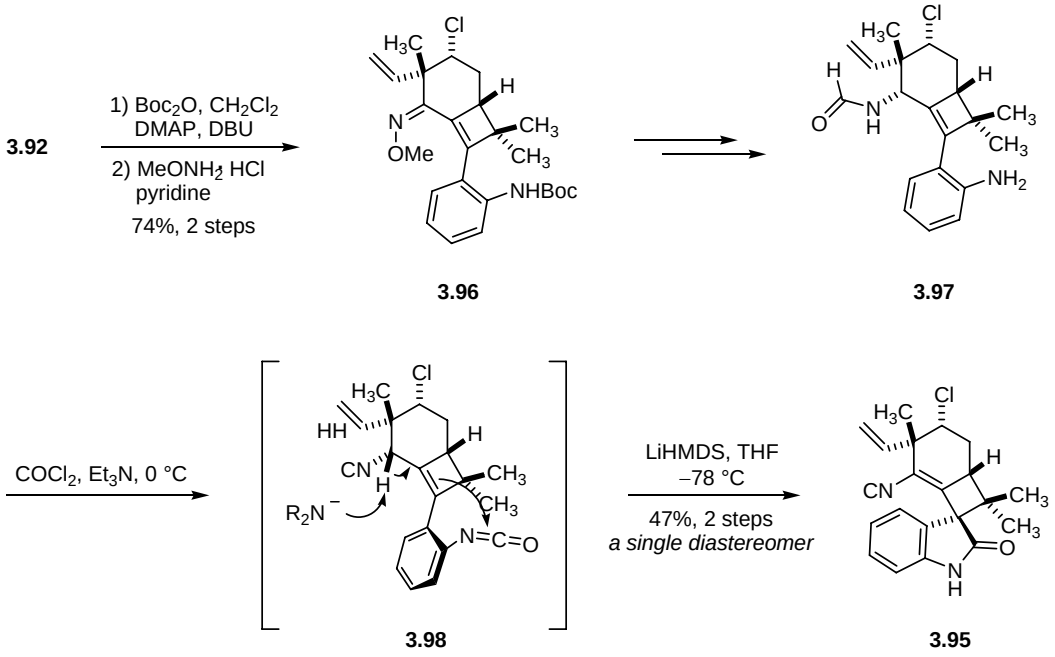
3.92 **3.93**

3.94 **3.95**

Given the unreactive nature of **3.94**, it was decided to functionalize the ketone prior to the construction of the oxindole. Toward this end **3.92** was converted to oxime **3.96**; however, this material was not sufficiently reactive toward the SmI_2 mediated reductive cyclization conditions (Scheme 3.18). Because of this problem, Wood and co-workers developed a complementary spirooxindole synthesis, which was closely related to the original strategy.[122] Intermediate **3.96** was converted in four steps to **3.97**, which was treated with phosgene. This resulted in the formation of **3.98** bearing the requisite isonitrile group as well an aryl isocyanate thus setting the stage for the pivotal spirooxindole formation. In the event, the isonitrile α-proton in **3.98** was readily deprotonated with LiHMDS at −78 °C to induce a cyclization of the olefin with the aryl isocyanate to afford the desired spirooxindole as a single diastereomer in 48% yield. Woods synthesis of this (±)-welwitindolinone A represents an excellent example of how the synthesis of complex natural products continue to inspire the development of new synthetic strategies. As in the case of Fukuyama's approach to Gelsemine, the

spirooxindole syntheses developed by Wood proceed in good diastereoselectivity but are highly specific to structures related to **3.94** and may not be readily applied to the synthesis of citrinadin A.

Scheme 3.18

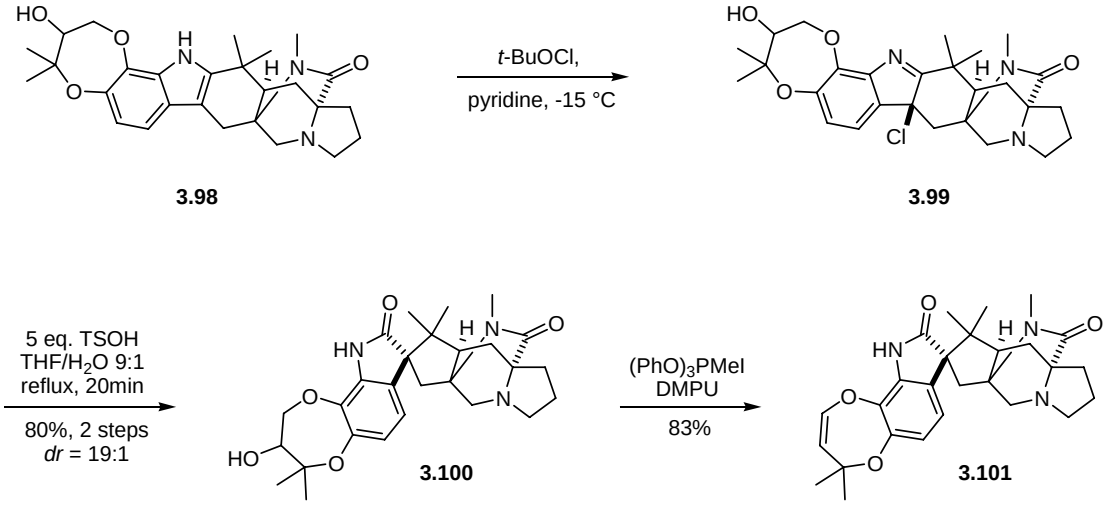


3.3.10 Spirooxindoles via Oxidative Rearrangement of Indoles

One of the most common methods for constructing spiro[pyrrolidine-3,3'-oxindoles], such as the one present in spirotryprostatin (**3.30**), is the oxidative rearrangement of an indoloquinolizidine.[26] Scheme 3.19 shows the last three steps in the total synthesis of (+)-paraherquamide B (**3.101**), by Williams and co-workers, in which an oxidative rearrangement was used to introduce the spirooxindole motif in excellent diastereoselectivity. Unlike in the synthesis of spiro[pyrrolidine-3,3'-oxindoles], there are not as many literature examples of the application of this transformation to substrates such as **3.98**, which do not have a nitrogen atom present in the ring appended to the

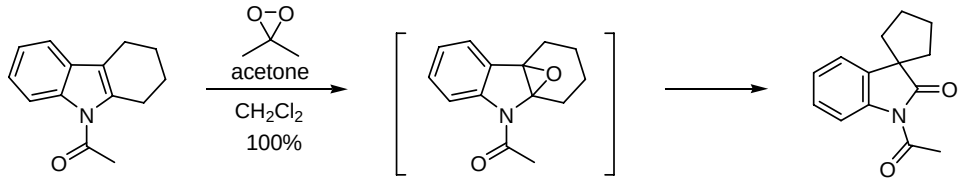
indole unit. While the chlorination step proceeded smoothly to give a single chloroindolinine **3.99**, the ensuing pinacol-type rearrangement was problematic. Commonly used procedures such as refluxing **3.99** in MeOH/H_2O/AcOH for 1 h,[123] or treating **3.99** with $AgClO_4$ and $HClO_4$[124] resulted in the formation of intractable reaction mixtures. After considerable experimentation, it was eventually discovered that **3.99** could undergo the desired hydration/rearrangement sequence by refluxing in the presence of TSOH in a 9:1 THF/ H_2O solvent mixture to give spirooxindole **3.100** in 80% yield (dr = 19:1). A disadvantage to the use of oxidative rearrangement is the incompatibility with olefins. As seen in Scheme 3.19 it was necessary to mask the olefin in the hydrated form and perform a dehydration at the last step of the synthesis. While this approach could potentially be applied to the synthesis of citrinadin A, it would require that facial selectivity can be achieved in the chlorination step based on the stereochemical elements that are already present in the molecule. This may not be as readily achieved in the case of citrinadin A as in **3.98**, which has a lactam ring partially shielding the back face of the indole as depicted in Scheme 3.19.

Scheme 3.19



Foote and co-workers demonstrated in 1993 that dimethyldioxirane (DMDO) was an effective epoxidizing agent for the C(2)-C(3) double of indoles bearing and acyl, siliyl, or methyl group on the nitrogen (Scheme 3.20).[125] They further demonstrated that while the resultant epoxides such as **3.103** are stable at low temperature, they rearrange to the oxindole upon warming to room temperature or upon exposure to silica gel chromatography. Foote was able to obtain X-ray structures of an indole epoxide, which indicated elongation of the bond between the C(3) carbon and the epoxide oxygen. This elongation presumably stems from benzylic stabilization and of the C(3) position, which also helps explain the high regioselectivity of the epoxide rearrangement.

Scheme 3.20



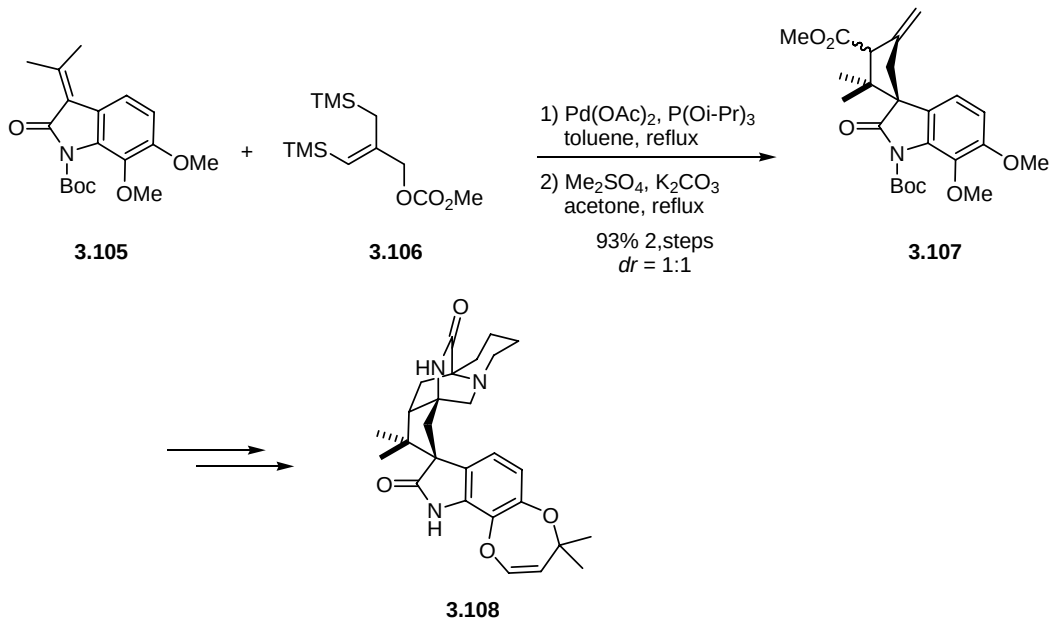
3.102 **3.103** **3.104**

While the rearrangement works exceedingly well for simple substrates such as **3.102**, the scope of this transformation was not investigated beyond simple 2,3-alkyl substituted indoles. Furthermore, to the best of our knowledge this rearrangement has never been applied to the synthesis of natural products. As will be discussed in detail in the following chapter, this transformation caught our attention, and it came to serve as the foundation on which we built our approach to the challenging spirooxindole motif of citrinadin A.

3.3.11 Spirooxindoles via Palladium Catalyzed Carboxylative TMM-Cycloaddition

The most recent contribution to the area of spirooxindole synthesis, and the one that perhaps holds the most promise for the synthesis of alkaloids such as citrinadin, was reported in 2007 by Trost and co-workers.[126] Their approach involved the application of a carboxylative palladium catalyzed trimethylenemethane (TMM) cycloaddition,[127] and was successfully applied to the first total synthesis of (±)-marcfortin B (**3.108**).[126] As depicted in Scheme 3.21, refluxing α,β-unsaturated indole **3.105** and TMM-donor **3.106** in the presence of $Pd(OAc)_2$ gave the spirooxindole **3.107** in 94% yield as a mixture (1:1) of diastereomers following methylation of the carboxylic acid. The formation of a diastereomeric mixture was of no consequence as this stereocenter was destroyed in the subsequent step.

Scheme 3.21



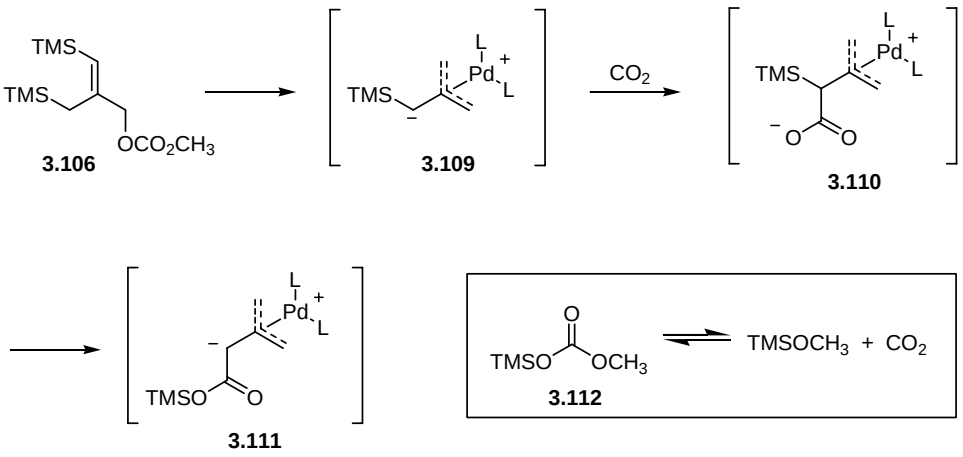
3.105 **3.106** **3.107**

3.108

The mechanism of this carboxylative variant of the TMM-cycloaddition is rather interesting and merits some comment. Exposure of TMM-donor **3.106** to $Pd(OAc)_2$

generates a π-allyl palladium complex that loses a TMS group through the nucleophilic attack by the carbonate anion to give **3.109** (Scheme 3.22). As shown in the box, the resultant methyl trimethylsilyl carbonate **3.112** presumably exists in equilibrium with methyl trimethylsilyl ether and CO_2, the latter of which can react with TMM intermediate **3.109** to give **3.110**. This intermediate can again undergo loss of a TMS group by the nucleophilic attack of a carboxylate anion to give the final reagent **3.111**, which subsequently undergoes the cycloaddition with **3.105**. Following cycloaddition, acid hydrolysis of the TMS ester then affords the final carboxylic acid.

Scheme 3.22



Trost's carboxylative TMM cycloaddition is an extremely powerful strategy to construct highly functionalized spirooxindoles. In particular the reaction proceeded in excellent yield in spite of the fact that the oxindole TMM acceptor was disubstituted in the β-position, which allowed for the incorporation of the gem-dimethyl group. A remaining limitation in this methodology is that the enantioselective version of this transformation has not yet been reported, although moderate success (63-84% ee) was

recently achieved in the non-carboxylative TMM cycloaddition.[128] As such, it would not be applicable to the asymmetric synthesis of **3.6** toward the synthesis of citrinadin A.

3.3 CONCLUSION

The discovery and isolation of biologically active and structurally complex oxindole alkaloids have spurred the development of novel methodologies for their efficient construction. Similar to alkaloids such gelsemine, welwitindolinone A, and marcfortin B, the recently isolated spiroindolinone alkaloid citrinadin A promises to gain the attention of the synthetic community due to its highly complex molecular architecture coupled with its useful biological activity.

One of the major synthetic challenges lies in the construction of the central five-membered ring in which all but one of the carbon atoms are fully functionalized and two adjacent quaternary centers are present. In contrast to spiro[pyrrolidine-3,3'-oxindoles] that contain a nitrogen in the five membered ring, the synthesis of spirooxindoles bearing an all-carbon framework has not been as extensively studied. The most general methods are radical cyclization, the asymmetric intramolecular Heck reaction, and most recently, the palladium catalyzed TMM cycloaddition. However, none of these methods can be readily applied to the enantioselective synthesis of **3.6**. The approach outlined herein also requires an efficient enantioselective synthesis of the trisubstituted piperidine fragment **3.7**. Notably, there are only a limited number of synthetic methods available for the preparation of 2,6-*trans* disubstituted piperidines. Finally, the proposed coupling of the spirocyclic ABC fragment **3.6** with the trisubstituted piperidine **3.7** will expand the limits of organozinc coupling chemistry.

The efficient enantioselective synthesis of spirooxindole fragment **3.6** and a trisubstituted piperidine fragment, as well as efforts toward the fragment coupling will be discussed in the following chapter.

Chapter 4: Studies Toward the Enantioselective Total Synthesis of Citrinadin A

4.2 INTRODUCTION

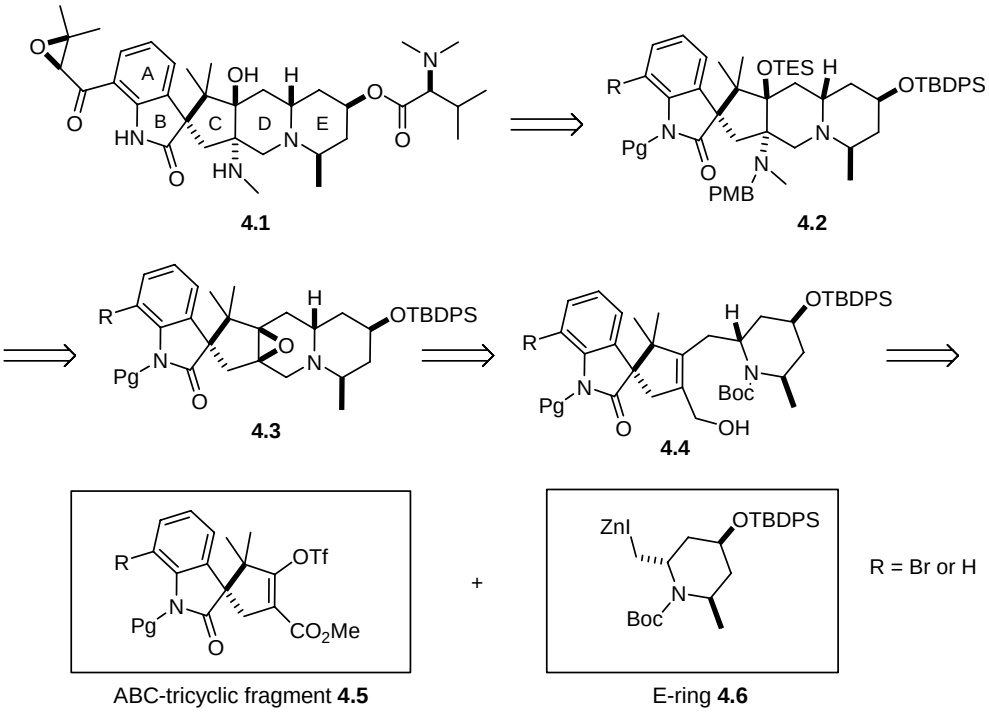
In the fall of 2002, when Kobayashi and co-workers reported the isolation and structure elucidation of the marine spiroindolinone citrinadin A (**4.1**), we were immediately attracted to this alkaloid because of its promising biological activity and its unique and highly complex molecular framework. We felt that the development of an efficient synthetic approach to this natural product would be of value for two reasons; (1) it would provide sufficient quantities amenable to extensive biological evaluation, and (2) it would offer significant synthetic challenges, which would inspire the development of useful and general solutions.

As discussed in Chapter 3, examination of the structural features of citrinadin A (**4.1**) revealed several synthetic challenges that needed to be addressed (Scheme 4.1). A major issue was the formation of the sterically hindered five-membered ring bearing the amino alcohol motif, which we envision coming from epoxide **4.3** via a trans-diaxial opening with an amine nucleophile. Another key step involved the coupling of alkylzinc species **4.6** with β-ketoester derived enol triflate **4.5** via a cupper catalyzed addition/elimination process. Jackson[129] and Knochel[96] have demonstrated the formation and subsequent cross coupling of aminoacid derived alkylzinc species, and Lipshutz have developed a coupling process in which alkylzinc reagents undergo 1,4-addition to α,β-unsaturated enoates bearing triflates in the β-position.[95] The 1,4-addition is then followed by β-elimination of the triflate to regenerate the double bond. This strategy, however, has

not been applied to systems as complex as in citrinadin, and its pursuit is likely to push the envelope of the current stage-of-the art.

The synthesis of the right hand fragment, the 2,4,6-trisubstituted piperidine **4.6**, may superficially appear simple; however, there are only a limited number of methods available for the efficient construction *trans*-2,6-piperidindes in an enantio- and diastereoselective manner.[97] Finally, the enantioselective synthesis of the tricyclic spirooxindole fragment **4.5** was thought of as a major challenge given the presence of the gem-dimethyl groups that would preclude the use of most existing methods as discussed in detail in Chapter 3. Additionally, the remaining available methods such as the carboxylative TMM-cycloaddition and radical cyclizations have not been performed in an enantioselective fashion. Hence, we decided to focus our initial efforts on the development of an efficient approach to enantiomerically pure tricyclic fragment **4.5**.

Scheme 4.1

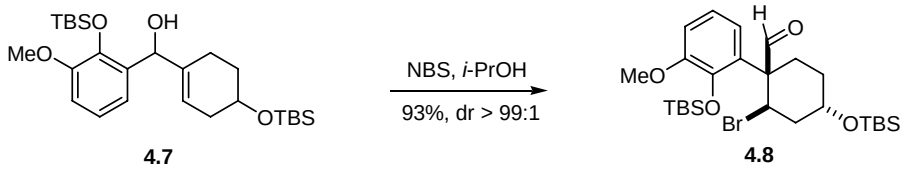


4.2 SPIROOXINDOLE SYNTHESIS VIA SEMI-PINACOL REARRANGEMENT

Tu and co-workers recently reported a novel NBS induced semi-pinacol rearrangement to generate quaternary centers in excellent diastereomeric ratio (Scheme 4.2).[130] It was envisioned that this methodology could be extended to the synthesis of spirooxindoles by designing an appropriate substrate such as **4.9** (Scheme 4.3). Exposure of **4.9** to NBS should lead to attack of "Br^{+}" on the less hindered face of the olefin leading to the stereospecific generation of spiro-derivative **4.11** via the intermediacy of **4.10**. Danishefsky showed in his synthesis of gelsemine that aryl carbamates such as **4.11** spontaneously react intramolecularly with aldehydes to form five-membered aminals such as **4.12**.[117] It might therefore be possible to go directly from **4.9** to **4.12** in a single

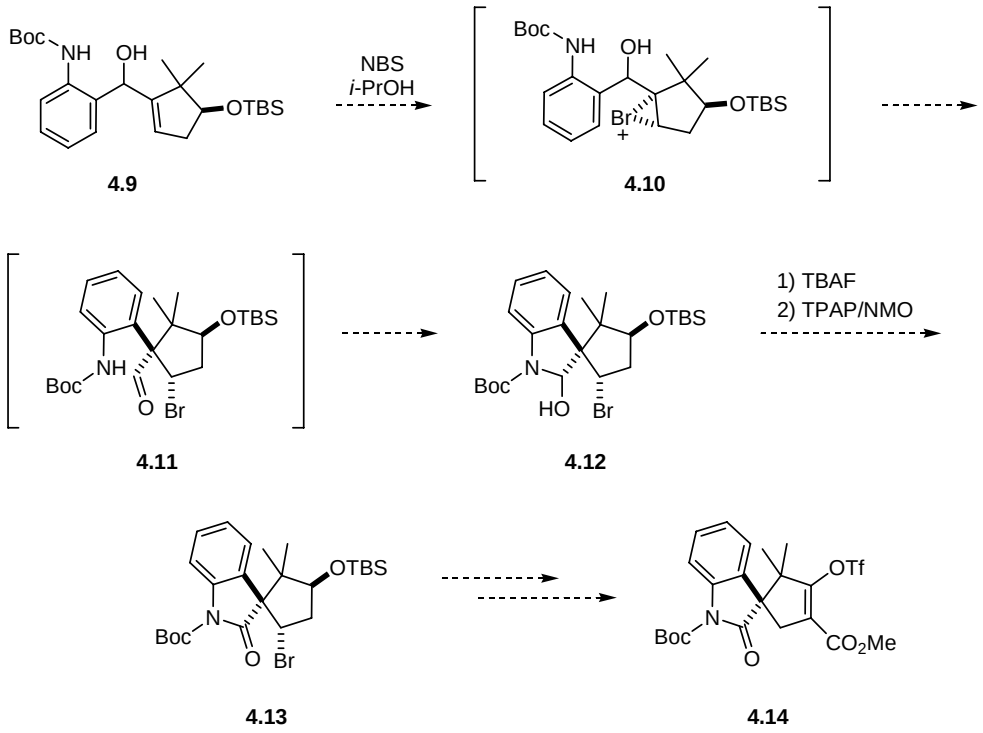
operation. Furthermore, Danishefsky demonstrated that aminals such as **4.12** are smoothly converted to the corresponding oxindole via oxidation with TPAP/NMO.[117]

Scheme 4.2



4.7 **4.8**

Scheme 4.3

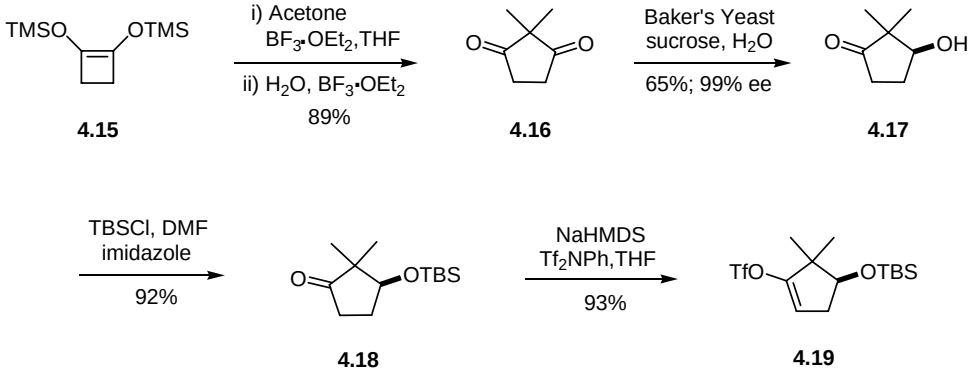


4.9 **4.10** **4.11** **4.12** **4.13** **4.14**

Preparation of the substrate **4.9** began with commercially available 1,2-bis-trimethylsilyloxybutene (**4.15**), which can be conveniently prepared on large scale via an intramolecular acyloin condensation of diethyl succinate.[131] Following published

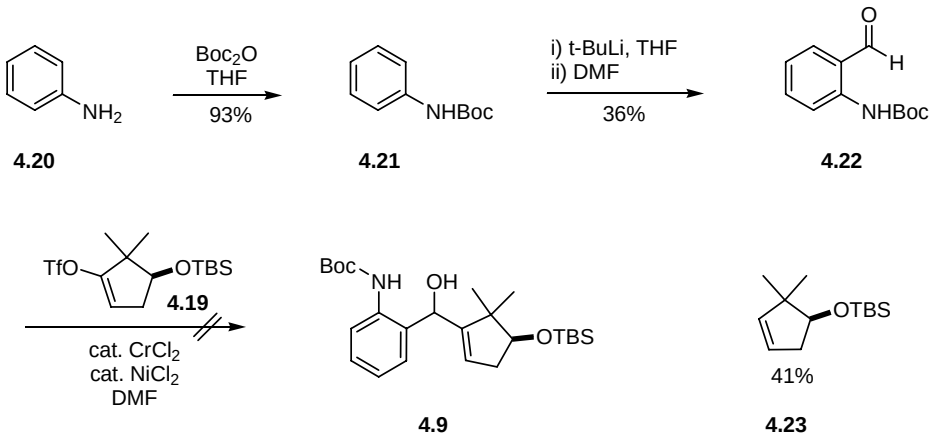
procedures, **4.15** was converted to **4.16** in 89% yield using a one-pot Mukaiyama aldol/ring expansion sequence (Scheme 4.4).[132] Next, asymmetry was introduced via a baker's yeast reduction to give ketol **4.17** in 44-65% yield.[133] This transformation has been reported to proceed with greater than 99% ee, although this was not verified by chiral HPLC. Following protection of the hydroxyl group gave the TBS ether **4.18** in 89% yield, the ketone moiety was deprotonated with NaHMDS and trapped with Tf_2NPh to afford the alkenyl triflate **4.19** in 93% yield.

Scheme 4.4



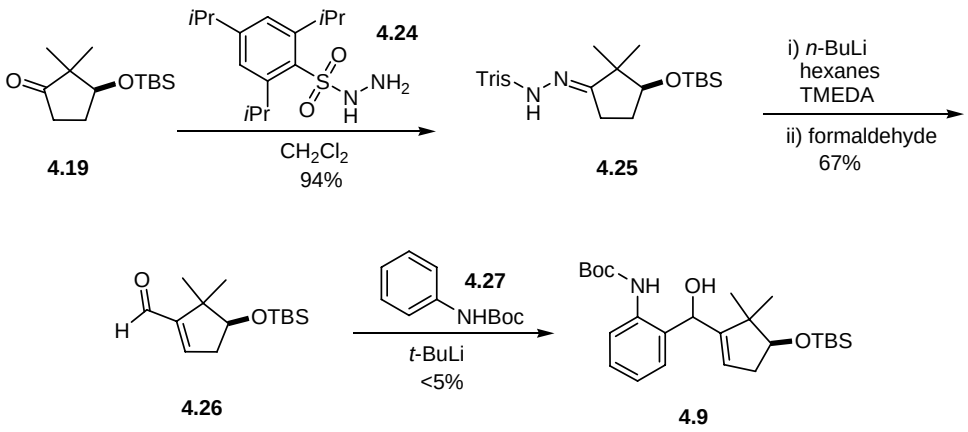
The aldehyde coupling partner **4.22** was prepared from the Boc-protected aniline **4.20** via *ortho*-directed metalation followed by formylation with DMF (Scheme 4.5).[134] Aldehyde **4.22** could only be obtained in 36% yield (55% was reported in the literature for this transformation; however, enough material could be secured to test the ensuing Nozaki-Hiyama-Kishi coupling. Unfortunately, exposure of triflate **4.19** and aldehyde **4.22** to stoichiometric Cr_2Cl_2 and catalytic $NiCl_2$ in DMF did not afford any of the desired product **4.9**. Rather, the reduced species **4.23** was isolated in 41% yield along with 45% recovered triflate starting material. The presence of **4.23** suggests that the alkenyl chromium reagent was indeed formed, but it did not react with aldehyde **4.22** and was simply quenched upon workup.

Scheme 4.5



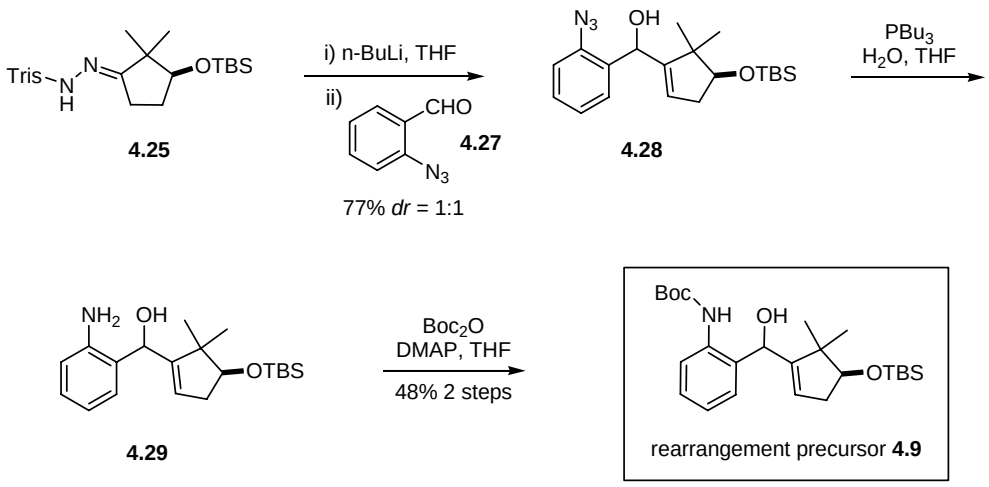
Since the alkenyl chromium reagent derived from **4.19** was not reactive enough to add to aldehyde **4.22**, we envisioned using the corresponding alkenyllithium species, which could be obtained from **4.18** via the Shapiro reaction (Scheme 4.6). After some optimization, ketone **4.18** could be smoothly converted to the trisylhydrazone **4.25** in 94% yield. Because of the acidic carbamate NH in **4.22**, the direct coupling of **4.25** with **4.22** was not pursued. Instead, a stepwise approach was taken in which **4.25** was first converted to enal **4.26** in 67% yield (Scheme 4.6). While this reaction worked well initially, subsequent attempts revealed that the reaction was not reproducible, and **4.26** could only be formed in low and inconsistent yields. In spite of this problem, sufficient quantities of **4.26** could be secured to attempt the coupling reaction with **4.21**. In the event, **4.21** was lithiated with *t*-BuLi and added to **4.26**; however, only a trace of the requisite substrate **4.9** was observed in the ^{1}H NMR spectrum of the crude reaction mixture. Given these problems, a third and final approach to the rearrangement substrate **4.9** was pursued

Scheme 4.6



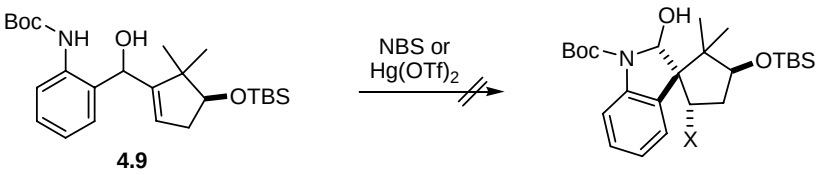
After some experimentation, it was eventually discovered that **4.9** could be accessed via the Shapiro reaction of **4.25** with *o*-azidobenzaldehyde (**4.27**) to afford **4.28** in 77% yield as a mixture (1:1) of diastereomers (Scheme 4.7). The stereochemistry of the secondary alcohol is inconsequential to the semi-pinacol rearrangement as the facial selectivity of the bromination of the olefin is presumably dictated by the stereochemistry of the silylether.[130] The order of addition of the reagents was found to be critical for the Shapiro reaction as the azide was unstable to strongly nucleophilic conditions. When *o*-azidobenzaldehyde was added as to the alkenyllithium intermediate generated from hydrazone **4.25**, the product could only be isolated in at most 22% yield. When the order of addition was reversed, however, the yield increased to 77%. With a scalable route to **4.28** in hand, the rearrangement precursor **4.9** could be accessed in just two additional steps: The azide was reduced via the Staudinger reaction to afford aniline **4.19**, which was treated with Boc_2O/DMAP to provide the requisite substrate **4.9** in 42% yield over the two steps.

Scheme 4.7



Having gained access to sufficient quantities of **4.9**, the stage was now set to explore the key semi-pinacol rearrangement. In the event, **4.9** was exposed to NBS in *i*-PrOH according to the conditions reported by Tu,[130] but only starting material was obtained after 1.5 h at room temperature (Table 1). The use of $Hg(COCF_3)_2$ was also explored, but again, only recovered starting material was obtained after 1.5 h at room temperature. Finally, the reaction was heated in a microwave reactor, but this resulted in loss of the Boc-group and extensive decomposition. It was postulated that the substrate might be too sterically hindered for the reaction to occur because of the presence of the gem-dimethyl groups. In light of these findings, the semi-pinacol approach was abandoned in favor of a different approach to the spirooxindole that was being pursued in parallel with the semi-pinacol approach (*vide infra*).

Table 4.1



4.9

4.12 X = Br
4.30 X = Hg

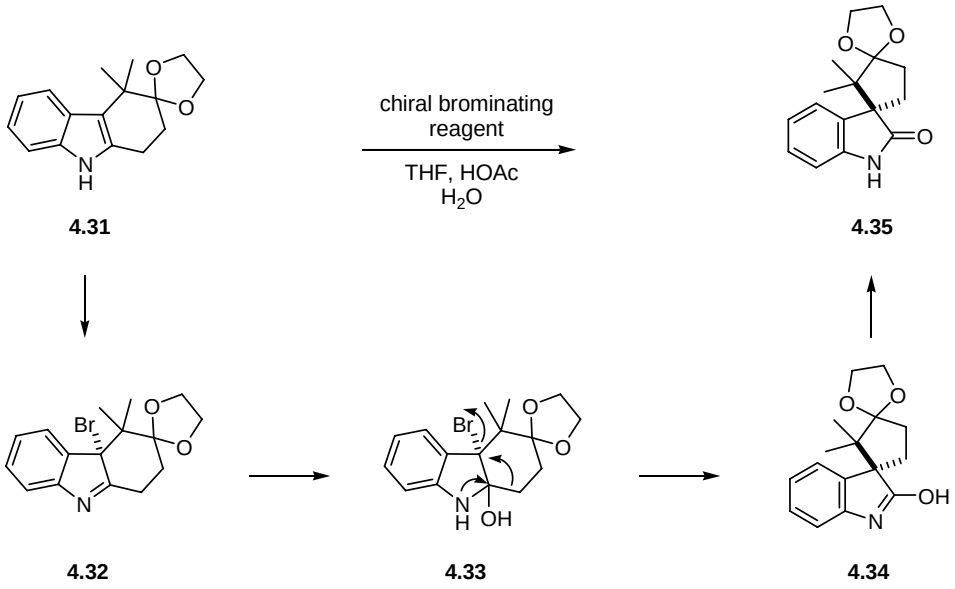
Entry	reagent	Solvent	Temp (°C)	Time	Result
1	NBS	*i*-PrOH	rt	1.5 h	only rsm
2	$Hg(OTf)_2$	THF	rt	1.5 h	only rsm
3	$Hg(OTf)_2$	THF	80 °C*	5 min	only rsm
4	$Hg(OTf)_2$	THF	150 °C*	5 min	decomp

*Heating was preformed in a microwave reactor

4.3 SPIROOXINDOLE SYNTHESIS VIA ASYMMETRIC OXIDATIVE REARRANGEMENT

An interesting possibility for the enantioselective construction of spirooxindoles would be to use a variant of the oxidative rearrangement of indoles. It was envisioned that this process could be rendered asymmetric by employing a chiral halogen source such as hypochlorite derived from menthol, or a C2-symmetric NBS derivative (Scheme 4.8). If facial selectivity can be achieved in the initial bromination or chlorination of the indole C(2),C(3)-double bond, enantioenriched spiro-oxindols may be obtained since the ensuing rearrangement is stereospecific.

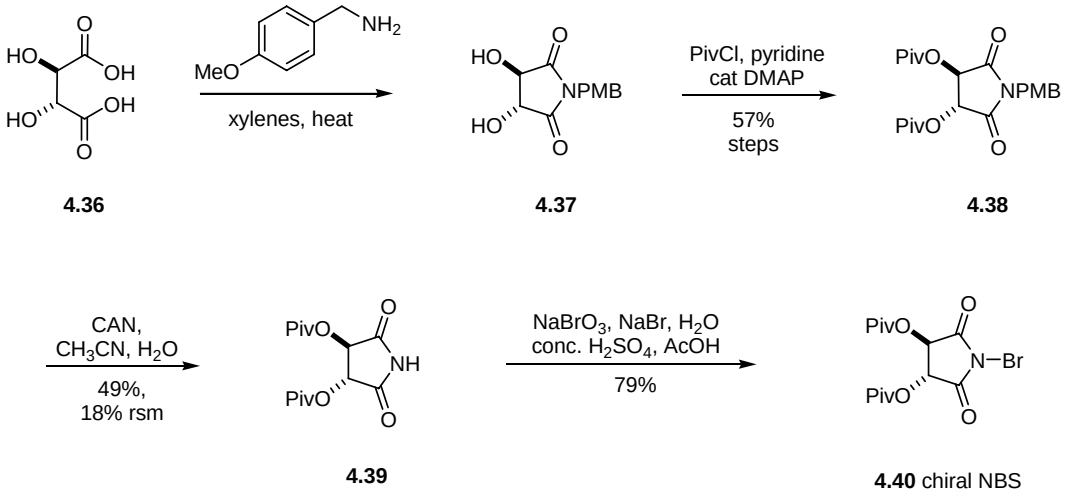
Scheme 4.8



4.3.1 Oxidative Rearrangement: Chiral NBS Approach

The preparation of a C2-symmetric chiral NBS-derivative was relatively straightforward (Scheme 4.9). A mixture of L-tartaric acid, *p*-methoxybenzyl alcohol and catalytic *p*-toluenesulfonic acid were refluxed in xylenes to afford **4.37**, which without purification was converted to the bis-pivalate derivative **4.38** in 57% yield over two steps. The PMB group was then oxidatively cleaved with ceric ammonium nitrate in 49% yield to give **4.39**. With pivalate **4.39** in hand, all that remained was the bromination of the imide function, which is typically carried out under strongly basic conditions. Since the application of such conditions would likely result in the hydrolysis of the pivalate esters, we turned to an alternative method reported by Fujisaki.[135] This protocol employs sodium bromate under mildly acidic conditions, and gratifyingly, when using this procedure, bromide **4.40** could be obtained in 79% yield.

Scheme 4.9

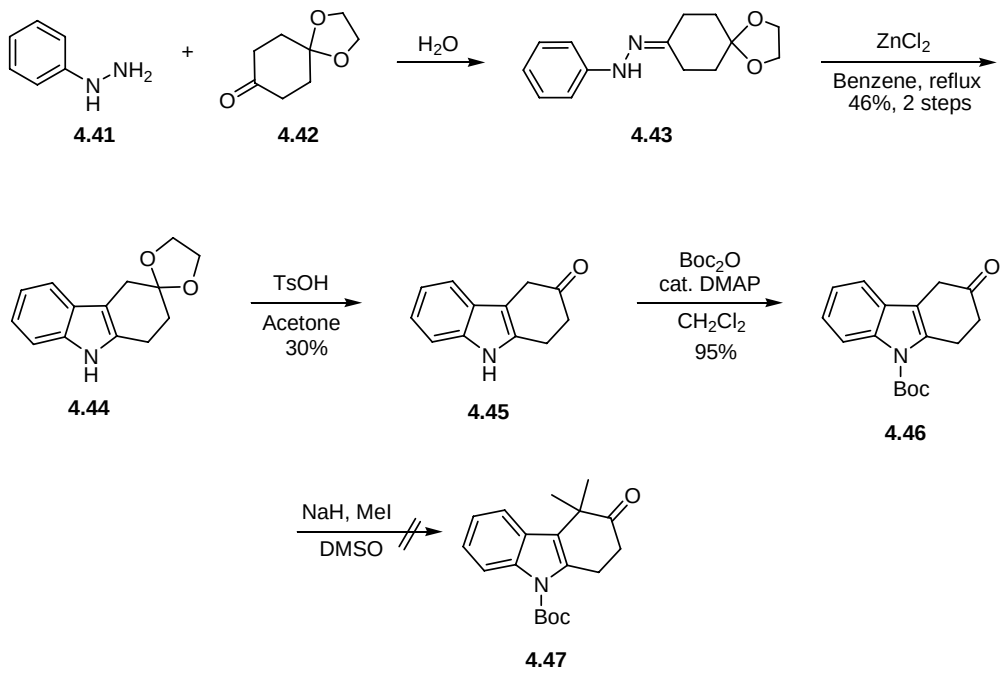


4.36 **4.37** **4.38**

4.39 **4.40** chiral NBS

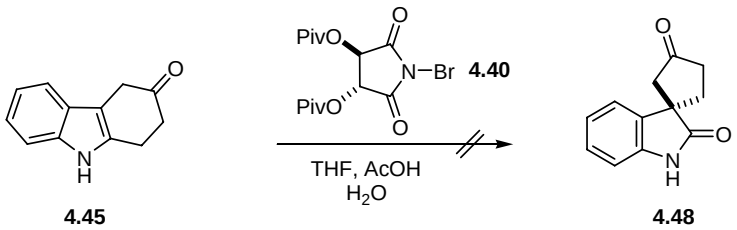
Next, an attempt was made to synthesize indole **4.47** in preparation for the oxidative rearrangement. Following literature procedures, **4.45** was prepared in three steps from commercially available phenylhydrazine (**4.41**) and 1,4-cyclohexadione monoketal (**4.42**), (Scheme 4.10).[136] After protecting the indole as the *t*-butyl carbamate, **4.46** was exposed to MeI and NaH in DMSO in an attempt to install the two geminal methyl groups. This transformation was unsuccessful as a complex reaction mixture was obtained.

Scheme 4.10



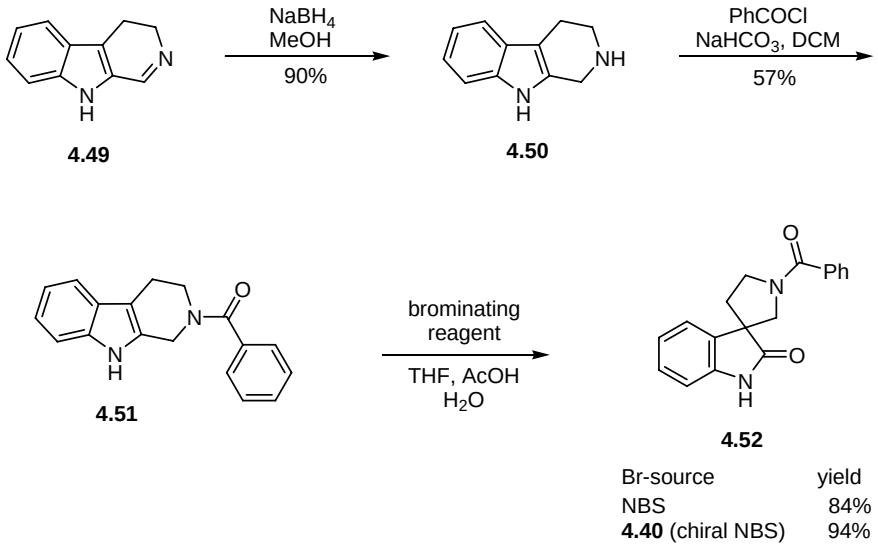
Since it was anticipated that the synthesis of **4.47** might be rather challenging, it was decided to first attempt the rearrangement on a simpler substrate such as **4.45**. Unfortunately, all attempts to effect the oxidative rearrangement using **4.40** resulted in intractable reaction mixtures (Scheme 4.11). This is perhaps not too surprising since we were unable to identify literature examples of an all-carbon framework undergoing this type of rearrangement with NBS.

Scheme 4.11



Although, the proposed oxidative rearrangement in its current form would not be applicable to the synthesis of citrinadin A, it was still worth exploring whether or not asymmetric induction could be achieved using the chiral NBS derivative **4.40**. Toward this end, a carboline derivative of the type that is known to undergo oxidative rearrangements with NBS was prepared according to published procedures as delineated in Scheme 4.12.[137] With **4.51** in hand, the oxidative rearrangement was attempted using the C2-symmetric NBS derivative **4.40**, and gratifyingly, the rearrangement delivered oxindole **4.52** in 94% yield. However, analysis of **4.52** by chiral HPLC and comparing the chromatogram to that of racemic **4.52** generated by the rearrangement of **4.51** with NBS, revealed that there was no detectable asymmetric induction. There are several conceivable explanations for this result. One possibility is that the chirality of **4.40** is too far removed from the indole C(2),C(3)-double bond in the transition state. Another explanation would be the possibility that the NBS derivative generates small amounts of bromine, which is the reagent that is actually carrying out the bromination.

Scheme 4.12

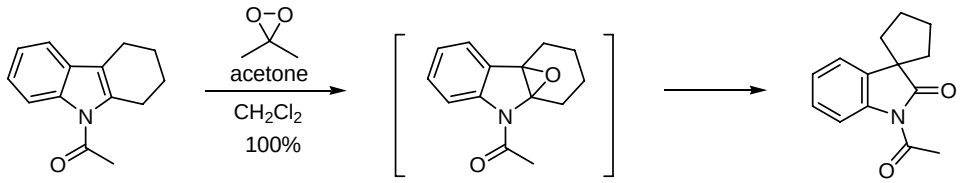


4.3.2 Oxidative Rearrangement: Shi Asymmetric Epoxidation Approach

At this point, two problems had to be addressed in order to make the strategy successful. First, a reagent had to be identified that is capable of effecting the rearrangement of a substrate such as **4.31**, which unlike **4.51** does not have a nitrogen in the ring appended to the indole. Second, the source of chirality had to be brought in closer proximity to the indole C(2),C(3) double bond in the transition state in order to achieve asymmetric induction. During a literature search, publications by Foote[125] and Adam[138] were identified, that inspired the solution two both of these problems. In 1993 and 1994, these workers demonstrated that dimethyldioxirane (DMDO) epoxidizes the indole C2-C3 double bond of *N*-acyl indoles such as **4.53** (Scheme 4.13). They further showed that while the resultant epoxide **4.54** was stable at low temperature, it rearranged to the oxindole **4.55** upon warming to room temperature or upon silica gel chromatography. Based on this precedent one can envision that if a chiral dioxirane such

as the one used in the Shi asymmetric epoxidation is employed, one might be able to achieve asymmetric induction.

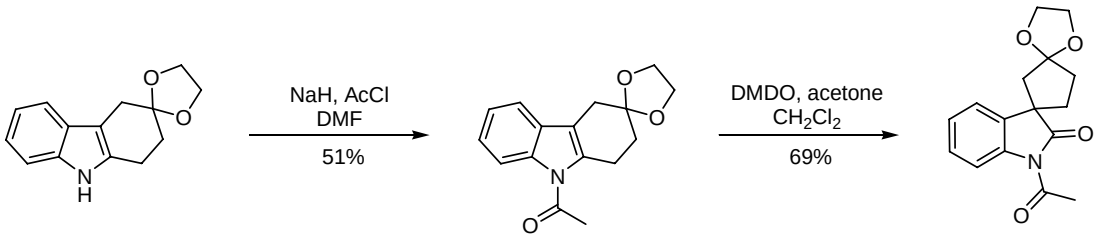
Scheme 4.13



4.53 **4.54** **4.55**

To examine the feasibility of this proposal, compound **4.44** was acylated to provide **4.56** as a model substrate. Subjecting **4.56** to the conditions reported by Foote afforded the spirocyclic indolinone **4.57** in 69% yield (Scheme 4.14). The successful oxidative rearrangement of a substrate containing an acetal was encouraging since Foote and co-workers did not provide any examples substrates bearing functionalization other than simple alkyl groups.

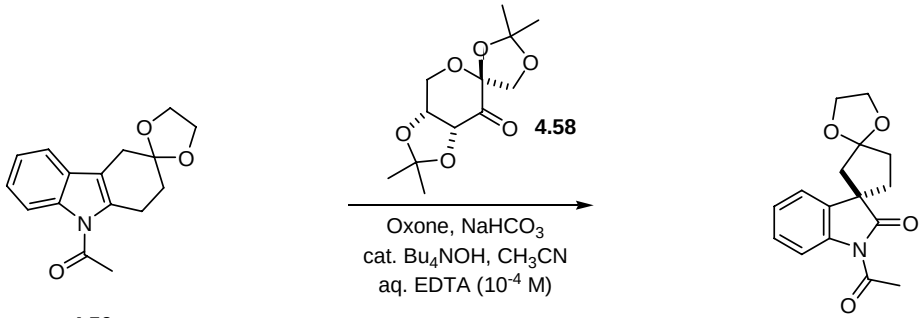
Scheme 4.14



4.44 **4.56** **4.57**

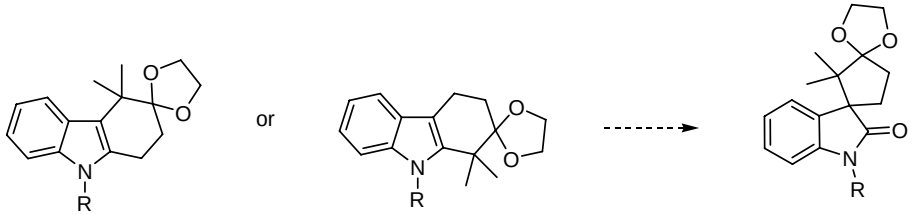
Next, **4.56** was subjected to the standard conditions used in the Shi asymmetric epoxidation reaction.[139] To our delight, the spirooxindole **4.57** could be isolated, albeit in only 7% yield, with the majority of the remaining mass balance being recovered starting material (Scheme 4.15). The product was then subjected to chiral HPLC analysis, and gratifyingly, an enantiomeric excess of 55-60% was observed.

Scheme 4.15



Having achieved proof of concept for the asymmetric oxidative rearrangement of a prochiral indole to an oxindole we decided to switch to the real system that would lead to the carbon skeleton of citrinadin rather than optimize a model system. Previous efforts had targeted **4.59** (Scheme 4.16), but the introduction of the gem-dimethyl groups through alkylation of ketone **4.46** was met with failure. It then became apparent that substrate **4.60**, which would be much easier to prepare, would give the same product in the oxidative rearrangement. The only difference would be that the opposite enantiomer would be obtained if the same chiral reagent was used.

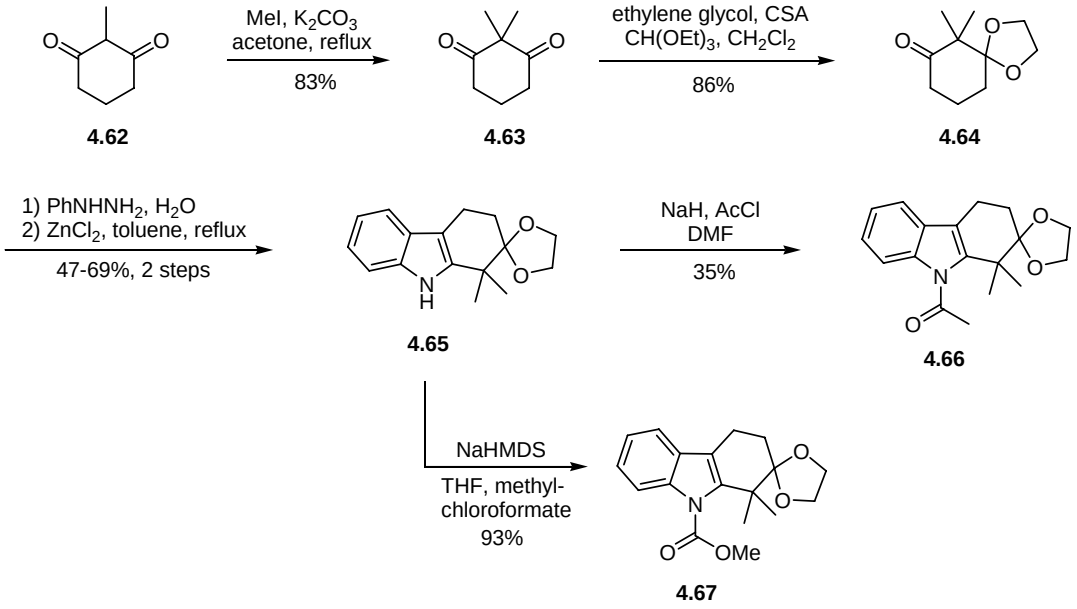
Scheme 4.16



Starting from 2-methyl-1,3-cyclohexanedione (**4.62**), methylation[140] followed by monoacetal formation[141] afforded ketone **4.64**, which was subjected to a Fisher indole synthesis (Scheme 4.17). In the event, refluxing a solution of the hydrazone derived from

4.64 and freshly fused zinc chloride in benzene according to the procedure reported by Britten,[136] gave indole **4.65** in 14% yield over the two steps. However, changing the solvent from benzene to the higher boiling solvent toluene, and increasing the amount of zinc chloride from one to two equivalents, improved the yield significantly, although some variability still remained (47%-69%). Following acylation of **4.65** with acetyl chloride as well as methyl chloroformate, we then turned our attention to the key asymmetric rearrangement of **4.66** and **4.67**.

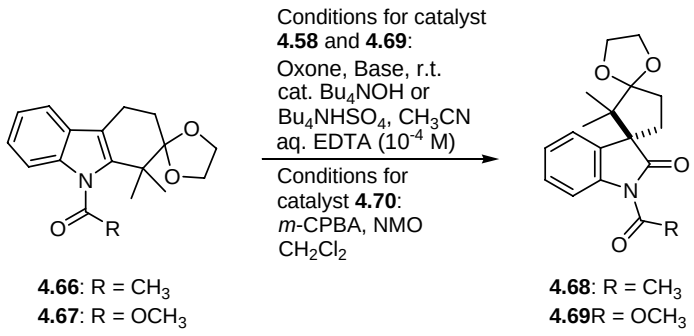
Scheme 4.17

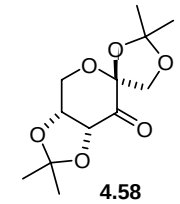


With the requisite substrates in hand, **4.66** was exposed to the same conditions as **4.56** (*vide supra*), although this reaction was run at room temperature to increase the rate of the reaction (Table 4.2). The desired product **4.68** was isolated in 15% yield together with 61% recovered starting material (entry 1). The product and starting material co-elute and could not be separated by chromatography. The yields were therefore determined by

integration of the ^{1}H NMR spectrum of the isolated mixture. Shi has reported that the reaction rate can be increased further by running the reaction at higher pH, which also prevents decomposition of the chiral ketone through Bayer-Villager reaction.[142] Buffering the reaction with K_2CO_3/sodium tetraborate (entry 2) gave oxindole **4.68** in 20% yield together with 40% recovered starting material. While this was the best result so far, the overall mass balance was lower than when the reaction was conducted at near neutral pH. This could presumably be due to the hydrolytic instability of the product imide, or even the *N*-carbamoyl indole starting material under the basic reaction conditions.

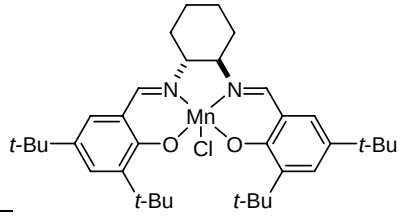
Table 4.2





Entry	Catalyst	R-group	Base	product / s.m.	yield (%)	rsm (%)
1	**4.58**	CH_3	$NaHCO_3$	1:4	15%	61%
2	**4.58**	**CH_3**	**K_2CO_3***	**1:2**	**20%**	**40%**
3	**4.58**	OCH_3	K_2CO_3*	1:3.6	n/a	n/a
4	**4.58b**	CH_3	$NaHCO_3$	1:2	7%	38%
5	**4.70**	CH_3	n/a	n/a	0%	56%

*(buffered with sodium tetraborate)



The effect of changing the indole protecting group from *N*-acetyl to *N*-methylcarbamate was then explored (entry 3). The ^{1}H NMR spectrum of the crude reaction mixture revealed a significant reduction in the amount of product formed as

compared to entry 2, so the product was not isolated. The ^{1}H NMR spectrum of **4.67** revealed that the indole aromatic protons were shifted further downfield as compared to **4.66**, suggesting that the methyl carbamate renders the indole ring more electron deficient than the acetate group. This in turn would cause the indole C(2),C(3)-olefin to be less reactive toward the dioxirane. Shi has reported that the more electron deficient chiral ketone **4.58b** is a better catalyst for epoxidations of electron deficient olefins such as enoates.[143] However, the oxidative rearrangement using this catalyst, which was prepared in two steps from **4.58**,[143] afforded the desired product **4.68** in only 7% yield (entry 4). Finally, an attempt was made to carry out the oxidative rearrangement using Jacobsen's catalyst **4.70**.[144] While this reaction typically works well with electron deficient olefins such as enones and enoates,[145] only starting material could be isolated from this reaction (entry 5.

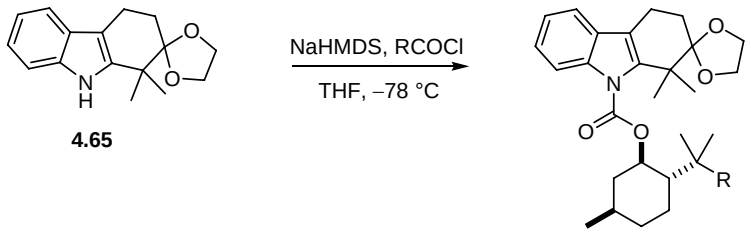
After exploring a variety of reaction conditions the desired spirooxindole **4.68** could only been obtained in a maximum of 20% yield (Table 4.2, entry 2). Presumably, the indole C(2),C(3) double bond is simply too hindered to react efficiently with the bulky dioxirane derived from **4.58**. As a result we decided to pursue a different avenue to achieve asymmetric induction. Nevertheless, this catalytic enantioselective approach to spirooxindoles may hold promise for less sterically hindered substrates, although this has not yet been explored.

4.3.3 Oxidative Rearrangement: Chiral Auxiliary Approach

It was envisioned that rather than using reagent control, one might be able to achieve facial selectivity in the epoxidation by using substrate control if a chiral auxiliary was placed on the indole nitrogen atom. Unlike the *N*-acetyl derivative **4.66**, the

carbamates **4.71** and **4.72** derived from menthol and 8-phenylmenthol could both be prepared in good yield being 80% and 65% yield respectively (Scheme 4.18).

Scheme 4.18



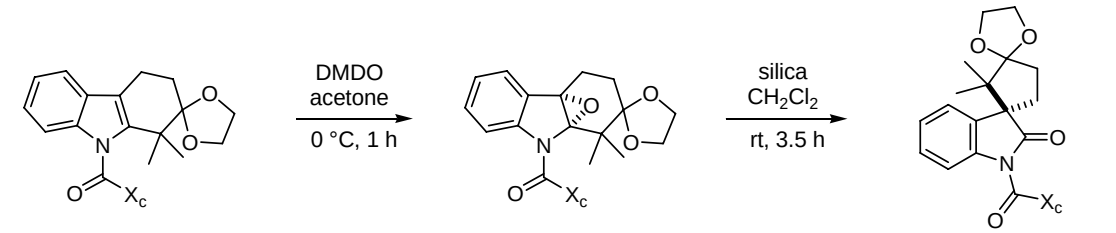
4.71 R = H: (80%)
4.72 = Ph: (65%)

With an ample supply of indole carbamates **4.71** and **4.72** in hand, we then turned our attention to the pivotal oxidative rearrangement. In the initial procedure, the reaction of **4.72** was typically run in CH_2Cl_2 or acetone for 2 h at 0 ˚C, at which point TLC analysis indicated that the all starting material had been consumed. The volatiles were then removed under reduced pressure, and the residue was purified by chromatography on silica gel to afford spirooxindole **4.76**. In these initial attempts to carry out the oxidative rearrangement, **4.76** was obtained in a 53% yield; however this yield was difficult to reproduce. Typically, the yields for this reaction ranged from 35-45%, and efforts were therefore directed toward optimizing this transformation. A clue to improving the yield was an observation in the ^{1}H NMR spectrum of the crude reaction mixture following the oxidation step. While TLC analysis of this material indicated a new product that co-spotted with the desired oxindole, ^{1}H NMR analysis revealed that none of the desired oxindole **4.76** was present in the reaction flask at that time. This observation suggested that the crude material was not the oxindole, but rather the indole epoxide **4.74**,

which underwent rearrangement to the oxindole **4.76** upon exposure to silica gel during TLC analysis or column chromatography (Table 4.3).

In order to test the hypothesis that the material isolated from the oxidation of **4.72** was the indole epoxide **4.74**, this material was dissolved in a mixture (4:1) of hexanes and EtOAc and stirred in the presence of silica gel at room temperature for 1 h. After removing the silica gel by filtration, ^{1}H NMR analysis indicated approximately 60% conversion of the intermediate to the requisite oxindole **4.74**, thus supporting the hypothesis that the unknown intermediate was indeed the indole epoxide **4.76**. Because the crude epoxide was exceedingly clean, it was assumed that it was the rearrangement of the epoxide that was the problematic step. A brief study of the effect of the solvent on the rearrangement was therefore undertaken (Table 4.3).

Table 4.3



X_c = menthol; **4.71** **4.73** **4.75** 78%; dr = 2:1

X_c = 8-phenylmenthol; **4.72** **4.74** **4.76** **78%; dr = 12:1**

isolated yields

solvent effect on epoxide rearrangment of **4.74**
mol% determined by ^{1}H NMR of the crude product mixture

solvent	unknonwn side product	8-phenyl-menthol	epoxide **4.74**	oxindole **4.76**
THF	trace	trace	>95%	0%
EtOAc	0%	trace	>95%	trace
Hexanes	14%	14%	0%	72%
Toluene	14%	11%	0%	75%
CH_2Cl_2	**11%**	**11%**	**0%**	**78%**

Epoxide **4.74** was stirred at room temperature in the presence of silica gel for 3.5 h in various polar and non-polar solvents. Upon filtration and removal of the volatiles, the crude reaction mixtures were analyzed by ^{1}H NMR, and the product distribution was reported as mol % (Table 4.3). Interestingly, these experiments revealed that the choice of solvent had a dramatic impact on the reaction. The use of polar solvents such as THF and EtOAc resulted mostly in recovered epoxide **4.74** and small amounts of side products, while non-polar solvents such as hexanes, toluene, and CH_2Cl_2 showed good conversion of **4.74** to **4.76**. CH_2Cl_2 appeared to be the best solvent resulting in 78% **4.76** along with 11% 8-phenylmenthol and 11% of an unknown side product. A potential explanation for the dramatic solvent effect in the 1,2-epoxide rearrangement of **4.74** to **4.76** is that silica is serving as an acid catalyst. Hence, a polar solvent more strongly coordinates to the acidic silica and disrupts the interaction between the epoxide with the silica, while non-polar solvents allows the epoxide to coordinate more strongly to the silica gel.

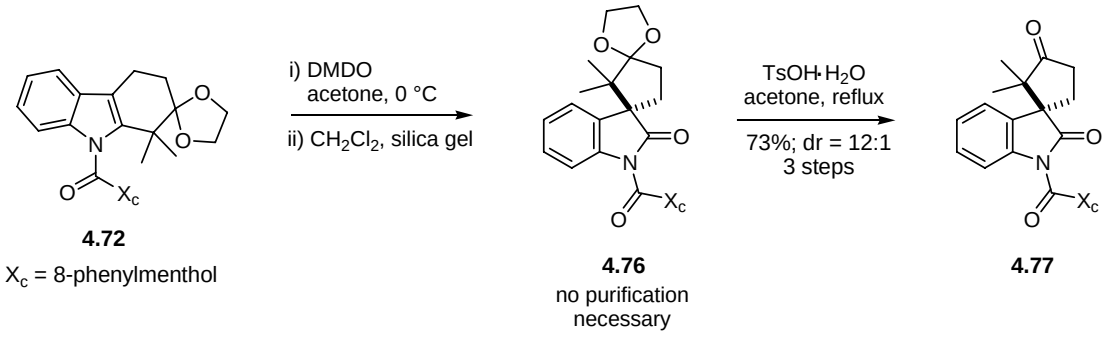
It is interesting to note that no 8-phenylmenthol was observed in the ^{1}H NMR spectrum of the crude epoxide **4.74.** This indicates that the 8-phenylmenthol-derived carbamate auxiliary is stable to DMDO, and that the partial fragmentation of the chiral auxiliary actually occurs during the rearrangement of step. Hence, a slight excess of DMDO can safely be used in the epoxidation step to drive the reaction to completion without any deleterious effects.

Using the optimized conditions the reaction was then performed on 50 mg scale with both the menthol- and 8-phenylmenthol-derived carbamates **4.71** and **4.72**. Gratifyingly, both reactions afforded the corresponding spirooxindoles **4.75** and **4.76** reproducibly in 78% yield. While the substrate bearing menthol-derived auxiliary

afforded the corresponding oxindole in a 2:1 diastereomeric ratio, switching to the 8-phenylmenthol derived auxiliary resulted in a significant increase in the diastereomeric ratio to 12:1.

Since the crude spirooxindole **4.76** was very clean, and since the small amount of 8-phenylmenthol impurity was difficult to remove by chromatography, an attempt was made to use the crude oxindole **4.76** directly in the ensuing deprotection step (Scheme 4.19). This three-step sequence was found to work very well and has been carried out multiple times on 0.5 g to 1.0 g scale. The yield is invariably above 70% for the three-step process after facile purification of **4.77** by chromatography.

Scheme 4.19

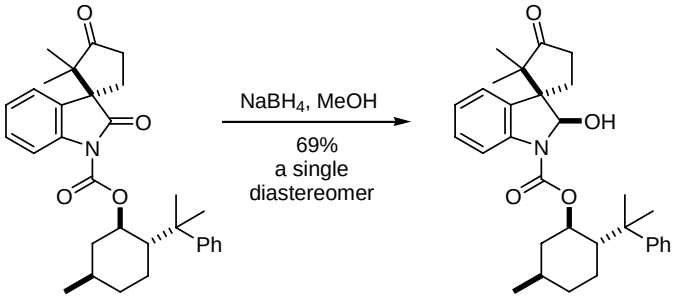


4.4 Completion of the ABC Fragment, and a Model Study of the Fragment Coupling

With an efficient and scalable route to **4.77** in hand, the next challenge was to determine the stereochemical configuration at the spirocenter. Compound **4.77** was obtained as a foam, and all efforts to crystallize this material were unsuccessful. A number of attempts were made to prepare a crystalline derivative; however, exposing **4.77** to reagents such as phenylhydrazine, *p*-nitrophenylhydrazine, and trisylhydrazide predominantly resulted in recovered starting material. On the other hand, subjecting **4.77**

to $NaBH_4$ delivered a new product **4.78** in 69% yield as a single diastereomer (Scheme 4.20).

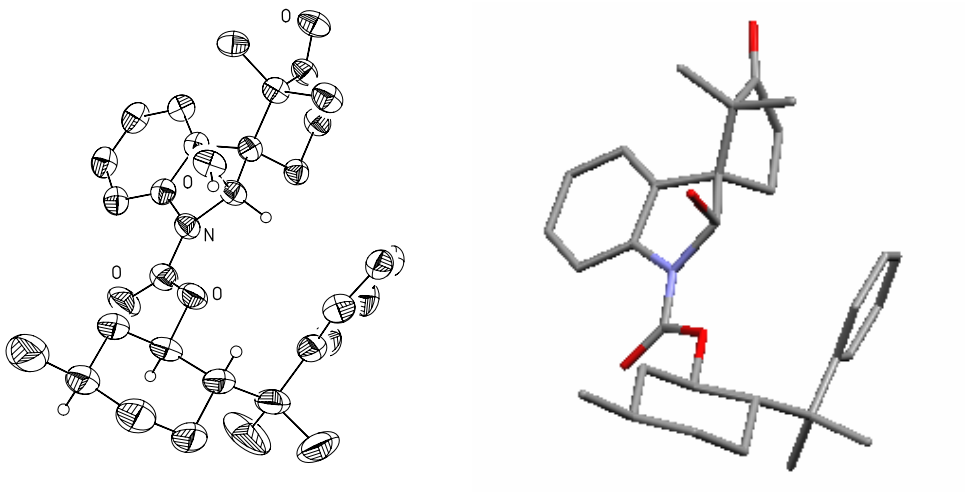
Scheme 4.20



4.77 **4.78**

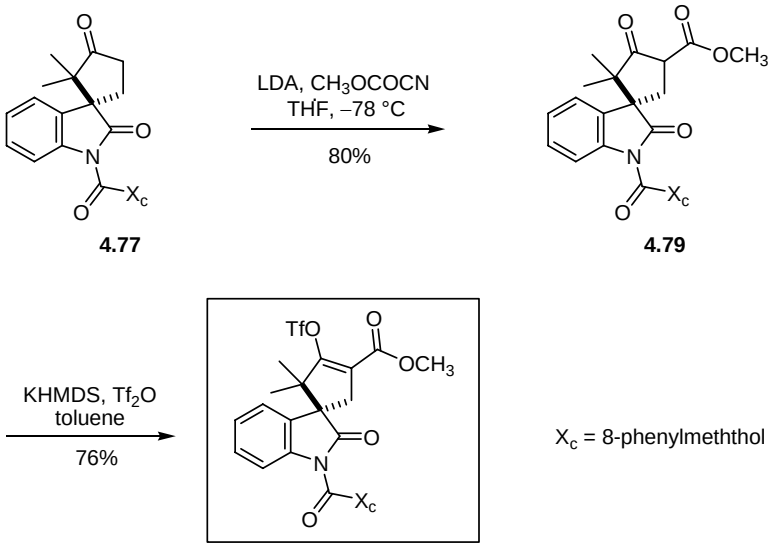
Interestingly, it was not the ketone that had been reduced but rather the carbonyl group of the oxindole. This is perhaps not too surprising since this carbonyl is part of an imide function. Nevertheless, aminal **4.78** was a crystalline solid and was submitted for single crystal X-ray analysis. To our delight X-ray structure of **4.78** revealed that the configuration at the spirocenter was indeed that of the natural product (Figure 4.1).

Figure 4.1 X-ray structure of spirooxindole **4.78**. Left: ORTEP plot, displacements ellipsoids are scaled to the 50% probability level; Right: X-ray plot generated by Mercury 2.1



Having developed an efficient approach to the spirooxindole **4.77** we were now in a position to complete the synthesis of the fully functionalized ABC coupling partner **4.80**. The next step involved the formation of the β-ketoester **4.79**. Acylation of the sodium enolate of **4.77** with methyl chloroformate gave exclusively the *O*-acylated product in 87% yield. On the contrary, the corresponding lithium enolate generated from deprotonation of **4.77** with LDA could be successfully acylated with Mander's reagent to afford **9** in 80% yield with only trace amounts of *O*-acylated material, which was readily removed by chromatography (Scheme 4.21). The β-ketoester **4.79** exists exclusively in the keto form as evident by ^{13}C NMR and was formed as a single stereoisomer, although the stereochemistry of the newly formed stereocenter was not determined. The formation of a single stereoisomer in this reaction suggests that the spirocyclic oxindole imparts a significant steric bias effectively blocking one face of the five-membered ring.

Scheme 4.21

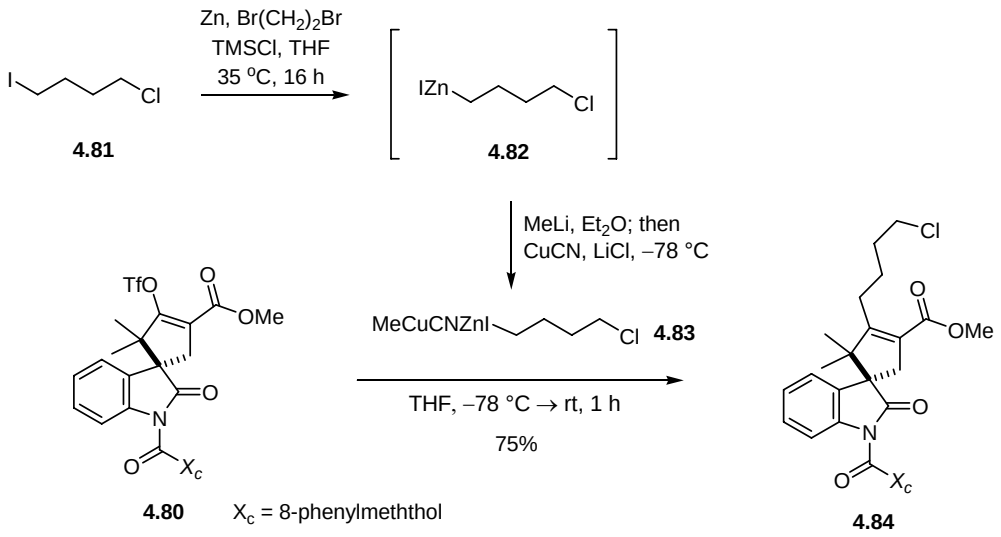


4.77 **4.79** **4.80** ABC Fragment: 10 steps

The final step in the synthesis of ABC-fragment involved the conversion of β-ketoester **4.79** to the corresponding triflate **4.80**. This transformation was first attempted by deprotonation of **4.79** with KHMDS followed by trapping the enolate with Comins' reagent. While this reaction resulted in a complicated mixture of products, deprotonation of **4.79** with NaH in CH_2Cl_2 followed by the addition of Tf_2O gave the desired triflate **4.80**, albeit in low to moderate yields. Unfortunately, the reaction was found to be irreproducible, and the yields varied from 10% to 53% depending on the batch of NaH that was used. The solution to this problem entailed using KHMDS in toluene as the base, and employing the more reactive electrophile Tf_2O. Using this reagent combination, requisite triflate **4.80** could be isolated in 76% yield in a reproducible manner (Scheme 4.21). The formation of triflate **4.80** thus completed the synthesis of the ABC tricyclic fragment of citrinadin, which proceeded in only ten steps and 14.6% overall yield from commercially available starting materials.

At this point it was desirable to explore the cross-coupling of triflate **4.80** via the proposed addition/elimination of a Knochel cuprate. This chemistry has been developed by Lipshutz using catalytic quantities of CuCN·2LiCl; however, none of the substrates in the study had branching in the γ-position.[95] Furthermore, prolonged reaction times were reported for substrates with only moderate steric hindrance. Since the rate of the reaction was found to be dependant on the loading of copper catalyst, we reasoned that by using stoichiometric amount of copper, the proposed coupling maight be possible in spite of the severe steric hindrance of **4.80**. Following the procedure of Knochel,[96] 4-chloro-1-iodobutane which is one of the iodides used by Lipchutz,[95] underwent direct insertion of zinc to give **4.82**, which in turn was converted to the more reactive dialkyl halide via addition of methyllithium at –78 ˚C (Scheme 4.22). Addition of a solution of CuCN·2LiCl then afforded the requisite species **4.83**, to which a solution of triflate **4.80** was added. The reaction was found to be quite rapid with complete consumption of **4.80** in less than an hour. Gratifyingly, **4.84** was isolated in 78% yield, demonstrating the viability of the exceedingly hindered triflate **4.80** as a fragment coupling partner.

Scheme 4.22

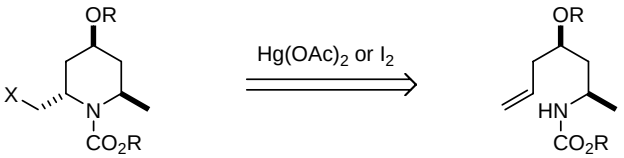


4.5 SYNTHESIS OF THE E-RING FRAGMENT

4.5.1 Electrophilic Cyclization Approach

Having succeeded in synthesizing of the ABC-tricyclic fragment **4.80** and demonstrating the viability of the fragment coupling in a model system, the next challenge involved the preparation of the E-ring coupling partner. Unlike in the case of 2,6-*cis*-piperidines, there are not nearly as many methods available in the literature for the enantioselective construction of 2,6-*trans* piperidines. As a result, the synthesis of the E-ring fragment **4.6** was actually considerable more challenging than initially anticipated. In one of the early approaches to the synthesis of **4.6**, we envisioned that the requisite iodide **4.85** could be accessed directly from olefin **4.87** via an iodo-cyclization.[100] Alternatively, a *trans*-selective mercury cyclization[98] might be employed to generate **4.86**, which in turn could be converted to the requisite iodide (Scheme 4.23).

Scheme 4.23

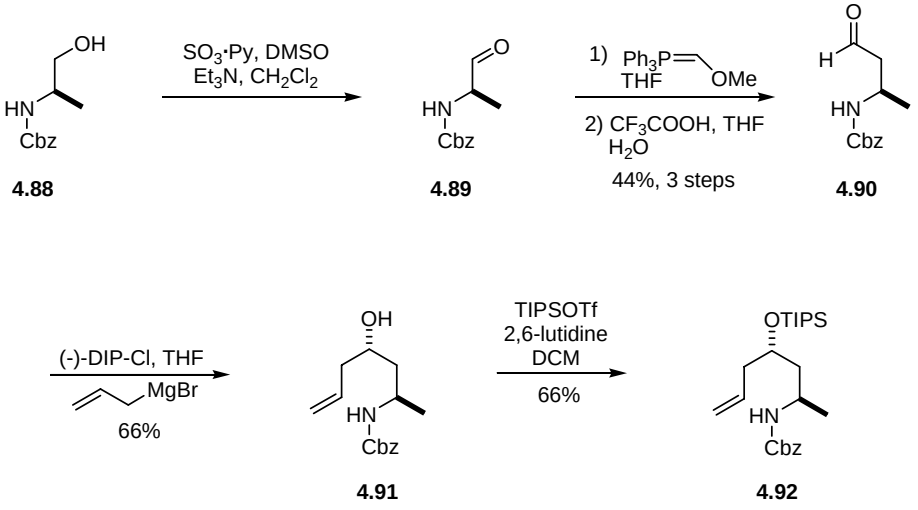


4.85 X = I
4.86 X = HgBr

4.87

The synthesis of the cyclization precursor **4.92** commenced with a Parikh-Doering oxidation of Cbz-alaninol (**4.88**),[146] followed by a two-step homologation to afford the known **4.90**[147] in 44% yield over the three steps (Scheme 4.24). Aldehyde **4.90** was then subjected to a Brown allylation to provide homoallylic alcohol **4.91** in 66% yield. This is the wrong stereochemistry of the hydroxyl group because the incorrect enantiomer of DIP-chloride was used. The mistake was not apparent until later in the synthesis via single crystal X-ray analysis of **4.95**. Nevertheless, following protection of the alcohol **4.91** as the TIPS-silyl ether to give **4.92**, we turned our attention to the key electrophilic cyclization to form the piperidine.

Scheme 4.24

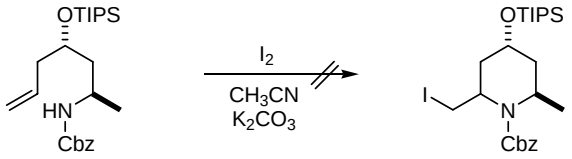


4.88 **4.89** **4.90**

4.91 **4.92**

Piperidine formation via iodocyclization of **4.92** was attempted first since it would generate the iodide **4.93** directly, resulting in an exceedingly concise synthesis of this fragment (Scheme 4.25). In order to force the reaction to go to completion it was necessary to use non-reversible, conditions, which can be achieved by the addition of K_2CO_3 to the reaction mixture. However, none of the iodide **4.93** could be isolated, and only an intractable reaction mixture was obtained.

Scheme 4.25



4.92 **4.93**

We next turned our attention to cyclization via amidomercuration since organomercurials can be directly converted to alkyl iodides.[99] Whereas the use of reversible conditions ($Hg(CF_3CO_2)_2$ in CH_3NO_2)[98] only resulted the recovery of starting material non-reversible conditions involving the use of $Hg(OAc)_2$ in THF[148] afforded piperidine **4.94** in 70% yield (dr > 10:1), (Scheme 4.26). With the organomercurial **4.94** in hand, its conversion to the iodide **4.93** was attempted. In the event, **4.94** was subjected to KI in refluxing CH_2Cl_2; however, none of the iodide **4.93** was observed. Instead, a different compound was isolated that had suffered loss of the Cbz protecting group. This material was crystalline a solid, and it was therefore submitted for single crystal X-ray analysis. To our surprise, the X-ray structure revealed that the new compound was in fact oxazolidinone **4.95**.

Scheme 4.26

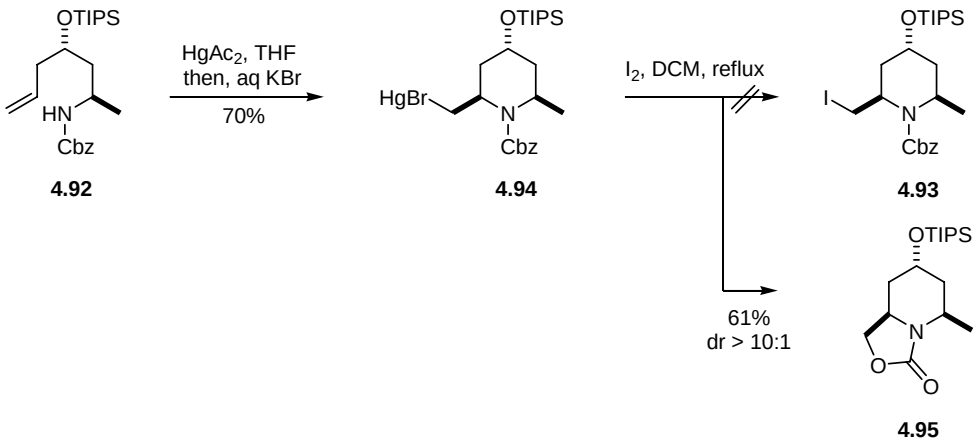
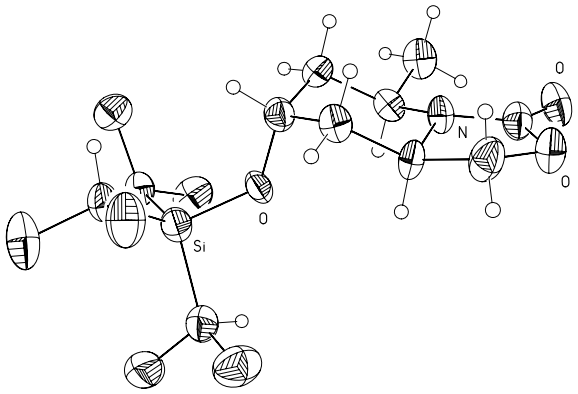


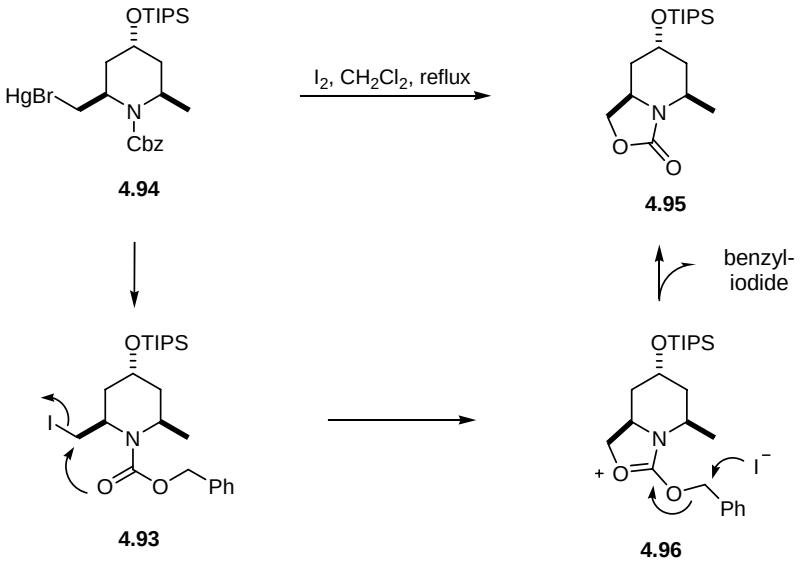
Figure 4.2 ORTEP plot of **4.95**. Displacement ellipsoids are scaled to the 50% probability level.



The formation of **4.95** was initially somewhat puzzling; however, we eventually developed a hypothesis as to how this reaction may be occurring. Presumably, the iodide **4.93** was is indeed formed, but it was not stable to the reaction conditions (Scheme 4.27). It is conceivable that **4.93** could undergo intramolecular cyclization by attack of the carbamate carbonyl oxygen onto the iodide to generate **4.96**. This intermediate could then further decompose to the give oxazolidinone **4.95**. If this mechanistic hypothesis is correct, one would also generate an equimolar amount of benzyl iodide, and indeed,

examination of the ^{1}H NMR spectrum of the crude reaction mixture of **4.95** revealsed signals that are consistent with the presence of benzyl iodide.

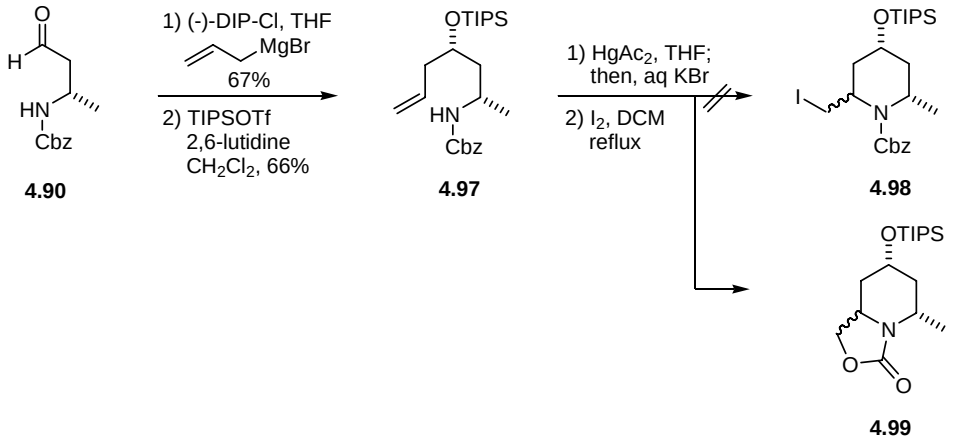
Scheme 4.27



As discussed above, the incorrect stereochemistry of the hydroxyl substituent was obtained during the Brown allylation. This in turn resulted in the exclusive formation of the 2,6-*cis* stereochemistry during the cyclization. It was therefore necessary to prepare substrate **4.97** with the correct relative stereochemical configuration since the stereochemistry may be an important factor for oxazolidinone formation. Substrate **4.97** was synthesized in an analogous manner to **4.92** and was submitted to the amidomercuration conditions (Scheme 4.28). The resultant crude organomercurial was treated with I_2 in refluxing CH_2Cl_2, but unfortunately, as was observed with **4.92**, the ^{1}H NMR spectrum of the crude reaction mixture indicated formation of the corresponding oxazolidinone. Furthermore, unlike in the case of **4.92**, **4.97** underwent the cyclization in a surprisingly low diastereomeric ratio (1:1.2). After observing oxazolidinone from both substrates **4.92** and **4.97**, we were mindful of the fact that it may be difficult to generate

the requisite precursor for the organozinc fragment **4.6**. Nevertheless, we felt that the oxazolidinone formation might be avoided if the iodide was formed under milder conditions that did not require heating of the reaction mixture. As such, we opted to continue to pursue the original strategy for coupling the fragments of citrinadin A.

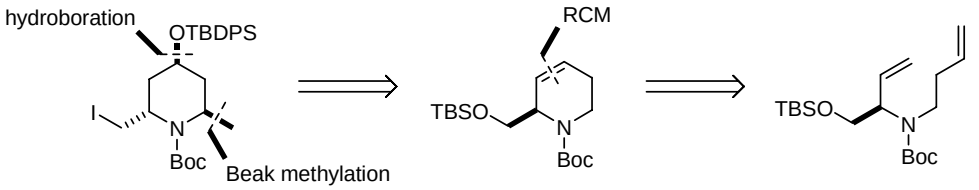
Scheme 4.28



4.5.2 RCM/Hydroboration Approach

Because of the difficulties that were encountered in the mercury cyclization, a different strategy was investigated. Beak has demonstrated that 2,6-*trans*-piperidines can be prepared in excellent diastereoselectivity via *ortho*-directed lithiation of Boc protected piperidines followed by alkylation,[102] and it was envisioned that this technology could be utilized to install the methyl group of piperidine **4.100 (**Scheme 4.29). The C(4) hydroxyl group would be introduced via hydroboration of the olefin **4.101**, where the use of the sterically demanding 9-BBN was expected to ensure the correct regiochemistry.[149] The 4,6-*trans* stereochemistry should result form approach of 9-BBN from the less sterically encumbered face through a transition state in which the boron approaches the olefin in an equatorial manner.[150] Finally, **4.101** would be obtained via RCM of olefin **4.102**.

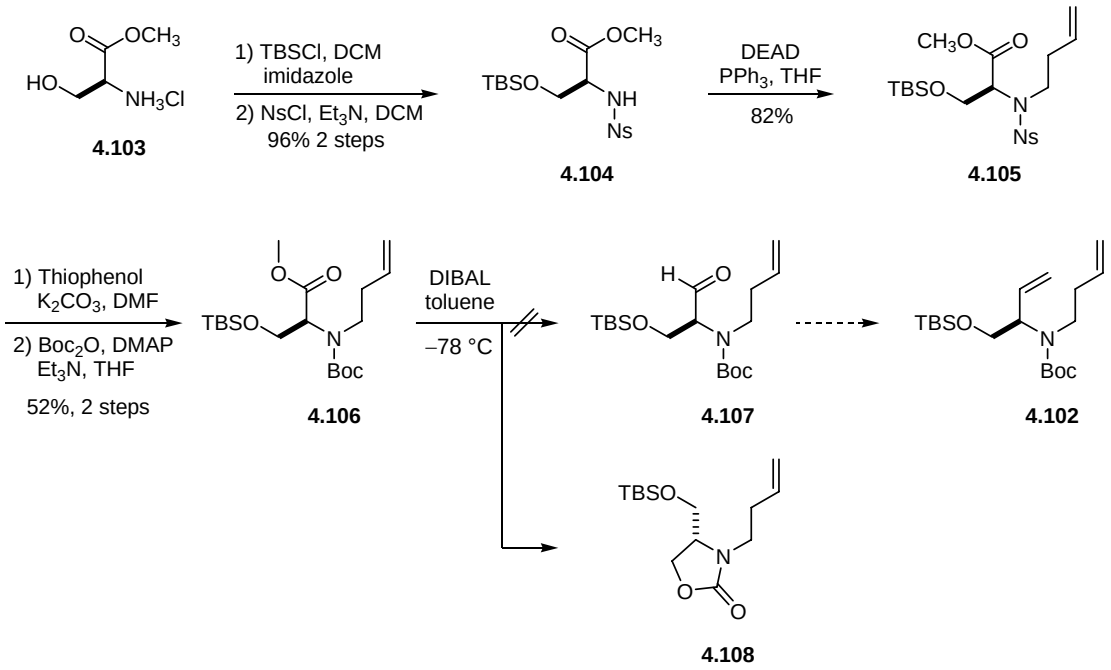
Scheme 4.29



4.100 **4.101** **4.102**

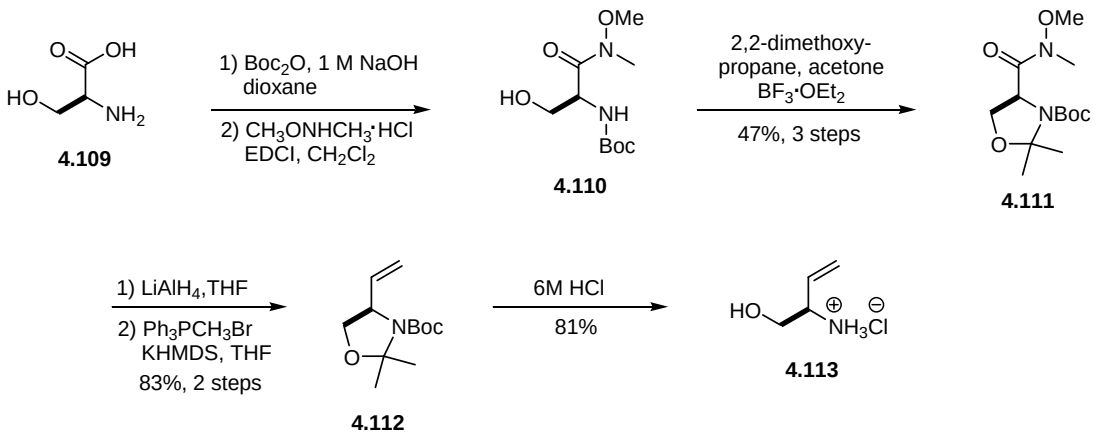
These studies were initially carried starting from L-serine methyl ester since the requisite D-enantiomer was more expensive. The plan was then to use the correct enantiomer once a successful synthesis of **4.100** had been achieved. Thus, synthesis of RCM precursor **4.102** commenced with the protection of the hydroxyl group of L-serine methyl ester as its TBS-ether followed by conversion of the primary amine to the nosyl amide to afford **4.104** in 96% overall yield (Scheme 4.30). This material was then subjected to a Fukuyama-Mitsunobu reaction[151] to install the homoallylic side chain in 82% yield. The nosyl group was readily removed by the action of phenyl thiolate, and the free amine was reprotected as its *t*-butylcarbamate **4.106** in 52% yield over the two steps.

Scheme 4.30



At this point, the ester was to be converted to the aldehyde in preparation for the ensuing Wittig olefination. However, subjecting **4.106** to DIBAL in toluene at –78 ˚C did not provide aldehyde **4.107**. The ^{1}HNMR spectrum of the crude reaction mixture only indicated a trace of aldehyde, and the majority of the material had suffered loss of the Boc group. It was postulated that over-reduction afforded an aluminum alkoxide, which may have cyclized onto the carbamate to afford **4.108**. It was therefore thought that it would be desirable to introduce the olefin at an earlier stage of the synthesis, and to that end, vinyl serine derivative **4.113** emerged as a suitable starting material. This compound is commercially available, which should ensure a relatively concise synthesis of piperidine **4.100** but it could also be prepared on large scale from the parent amino acid following a facile six-step sequence described by Taylor (Scheme 4.31).[152]

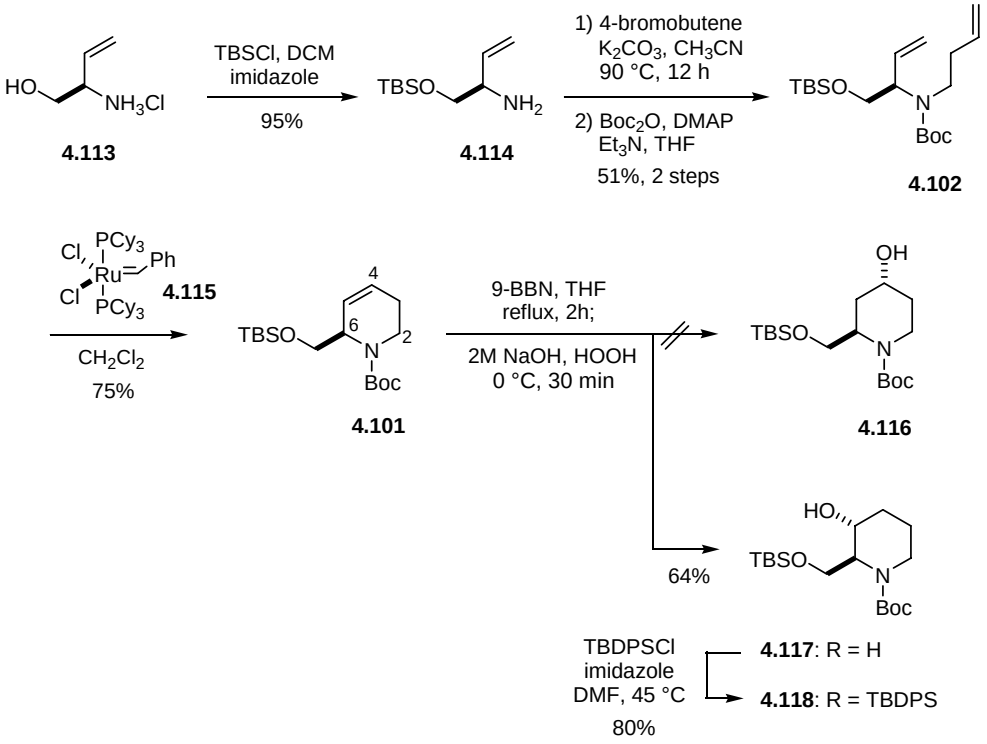
Scheme 4.31



4.109 **4.110** **4.111** **4.112** **4.113**

With vinyl serine derivate **4.113** in hand, the synthesis of **4.100** commenced with the protection of the primary alcohol as its TBS ether to give **4.114** in 95% yield (Scheme 4.32). The homoallylic side chain was then installed via monoalkylation of the primary amine with 4-bromo-1-butene, followed by Boc protection to afford **4.102** in 51% overall yield. It is interesting to note the alkylation of the corresponding Boc-protected derivative of **4.114** only resulted in recovered starting material, which is in accordance with the literature.[153] This is presumably due to competitive E_2 elimination of 4-bromobutene.

Scheme 4.32



Having established an efficient route to RCM precursor **4.102**, this material was then subjected to 5 mol % Grubbs I catalyst (**4.115**) to furnish **4.101** in 75% yield. The next challenge involved the introduction of the hydroxyl group in the 4-position via hydroboration. In the event, a solution of **4.101** and excess 9-BBN in THF was heated under reflux overnight to afford a mixture of compounds, the major of which was isolated in 64% yield. This material was initially believed to have the desired regiochemistry based on its COSY spectrum. However, we were surprised to discover at a later stage in the synthesis that this structural assignment was incorrect by obtaining the X-ray structure of **4.121** (*vide infra*).

Unaware that the hydroboration of **4.101** had resulted in the undesired regiochemistry, the synthesis of **4.100** was continued. After protecting the newly introduced hydroxyl group as its TBDPS ether to give **4.118**, attention was focused on the

pivotal alkylation to introduce the C(2) methyl group. Following the protocol by Beak,[102] **4.118** was lithiated with *sec*-BuLi and alkylated with iodomethane to afford **4.119**, which was isolated as a single stereoisomer in 54% yield (Scheme 4.32). The yield could likely be improved further by using dimethyl sulfate instead of iodomethane, since dimethyl sulfate has shown to be a superior alkylating reagent in many cases for this reaction.[102]

With all the stereocenters now installed, it only remained to elaborate the TBS ether to the requisite iodide. But before going any further, it was necessary to establish the stereochemistry of the two newly formed stereocenters as well as the position of the hydroxyl group. With this goal in mind, **4.119** was treated with TBAF to afford diol **4.120** in 75% yield (Scheme 4.33). The plan was to acylate both hydroxyl groups to afford the bis-*p*-nitrobenzoate. Unexpectedly, when exposing **4.120** to *p*-nitrobenzoyl chloride and DMAP in CH_2Cl_2, a different compound was isolated in 45% yield, the ^1H NMR spectrum of which was consistent with oxazolidinone **4.121**. Nevertheless, this compound was a crystalline solid and was submitted for X-ray analysis. However, the X-ray structure revealed that the undesired regiochemistry had been produced as the major isomer in the hydroboration reaction.

Scheme 4.33

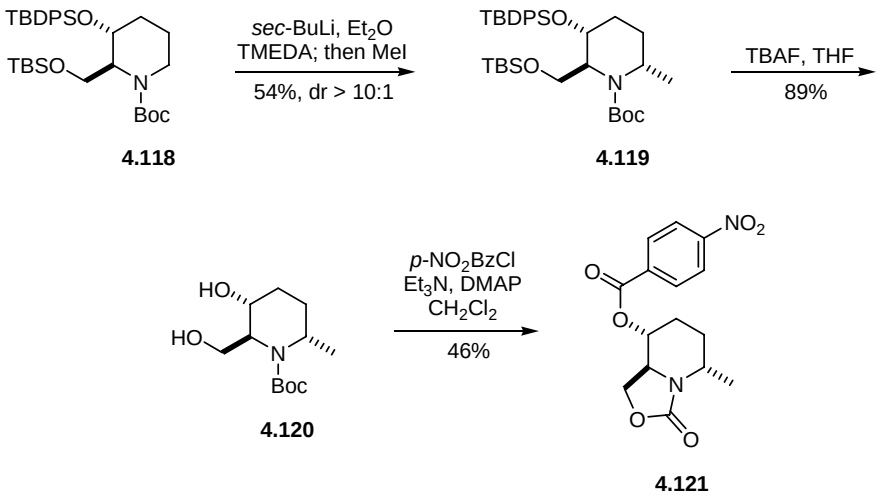
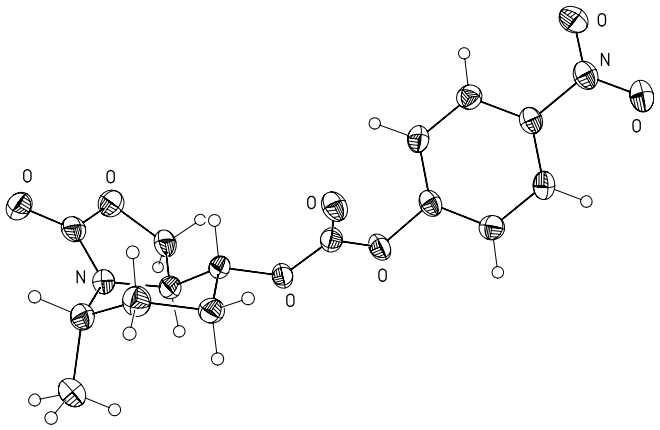


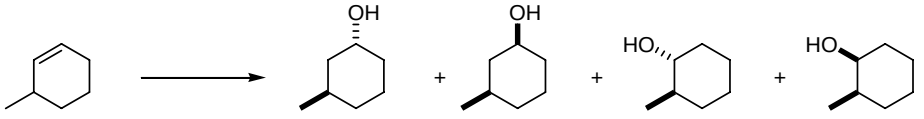
Figure 4.3 ORTEP plot of **4.121**. Displacement ellipsoids are scaled to the 50% probability level.



The unexpected regiochemical outcome of the hydroboration of **4.101** merits some discussion. It was hypothesized that hydroboration of **4.101** to afford **4.116** with the hydroxyl group in the 4-position would be preferred in order to minimize steric interactions between 9-BBN and the silyloxymethyl substituent in the transition state. This assumption was based on literature precedent in which 1-methylcyclohexene (**4.122**)

was hydroborated with various borane reagents (Scheme 4.34). In this study, the hydroboration of **4.122** using 9-BBN resulted a 80:20 ratio of regioisomers favoring introduction of the oxygen in the 3 position.[154]

Scheme 4.34

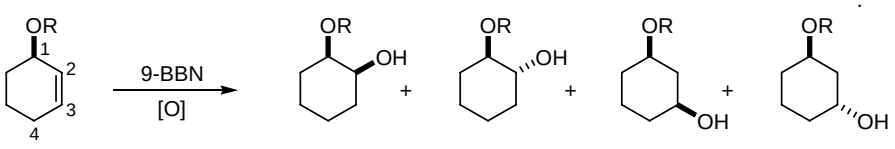


4.122 **4.123a** **4.123b** **4.124a** **4.124b**

BBH_3	32:18:34:16
Sia_2BH	25:27:30:18
9-BBN	40:40:20:0

On the other hand, Evans demonstrated that electronic effects can play a major role in determining the regiochemical outcome of hydroborations of cyclohexene derivatives.[155] Contrary to what would be expected based on steric arguments, hydroboration of **4.125b** gave **4.127b** as the major products in which the hydroxyl group has been introduced in the 2-position (Scheme 4.35). It therefore appears that the electronic effects resulting from the presence of the electron withdrawing oxygen substituent overrides the steric preference for introducing boron at the sterically less demanding C(3) carbon.

Scheme 4.35



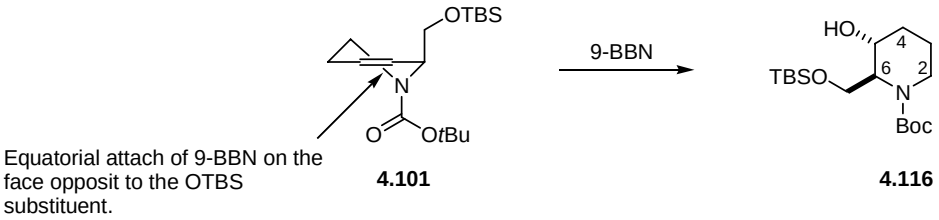
4.125a R = Bn
4.125b R = Bn

4.126 **4.127** **4.128** **4.129**

R = Bn	0 : 68 : 19 : 13
R = TBS	0 : 74 : 13 :13

A similar explanation may account for the regiochemistry in the hydroboration of piperidine **4.101**. Introduction of boron at C(4) would place a partial positive charge at C(5) adjacent to C(6) in the transition state. Since C(6) is already electron deficient due to the presence of the carbamate this would be unfavorable. Furthermore, unlike in the case of 1-methyl cyclohexene in which the methyl group is planar, in the case of carbamate **4.101**, the silyloxymethyl group is likely forced into the axial orientation in order to minimize pseudo-A(1,3) strain with the carbamate (Scheme 4.36). As such, the silyloxymethyl group may be less a determining factor, allowing the regiochemistry to be dictated predominantly by electronic factors.

Scheme 4.36



A known solution to this problem that could be applied to override the electronic preference for hydroboration in the 5-position would be to perform the hydroboration with pinacolborane in the presence of Wilkinson's catalyst.[155] This reaction was attempted on **4.101** several times, but in all cases only starting material was recovered. It was therefore decided that a new approach to the piperidine fragment would be needed.

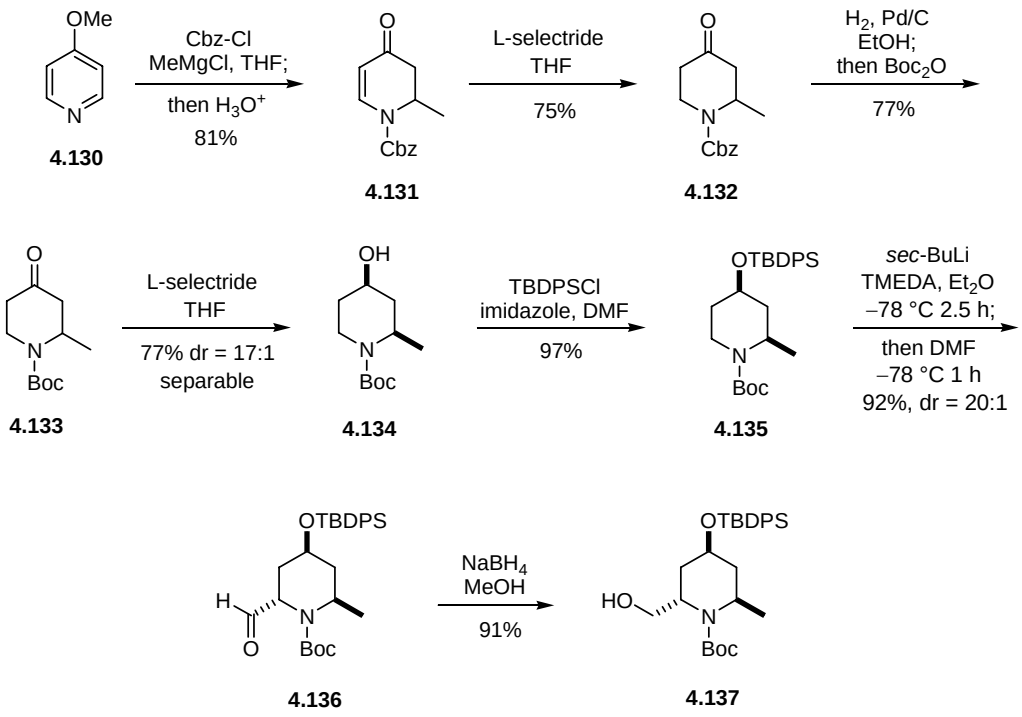
4.5.3 Acyl Pyridinium Ion Approach: Successful Racemic Synthesis of the E-ring

A possible approach to the requisite 2,4,6-trisubstituted piperidine **4.100** would involve an application of Comins' technology[103] coupled with ortholithiation chemistry developed by Beak.[102] The use of Comins' enantioselective piperidine synthesis in this

case, however, would render the sequence rather lengthy. Therefore, a synthesis of racemic material was initially pursued, hoping that an alternative to the Comins' protocol eventually could be developed once a proof of concept for the fragment coupling of **4.6** and **4.80** had been established.

The synthesis of **4.137**, which is outlined in Scheme 4.37, commenced with the addition of methylmagnesium chloride to the pyridinium salt generated by the reaction of 4-methoxypyridine (**4.130**) with Cbz-Cl. Upon acidic workup, piperidone **4.131** was obtained in 81% yield and used directly in the next step without further purification. When, **4.131** was subjected to a 1,4-reduction with L-selectride, **4.132** was isolated in 75% yield. At this point, the Cbz-group was replaced with a Boc-carbamate, which would be needed later in the synthesis in the *ortho*-lithiation step. In the event, hydrogenolysis of **4.132** in ethanol gave the corresponding secondary amine, which was not isolated but treated directly with Boc_2O to give **4.133** in 77% yield in a one-pot operation. Following stereoselective reduction of the ketone (77% yield, dr = 17:1) and protection of the resultant alcohol as a TBDPS ether (97% yield), the stage was set for the key *ortho*-directed lithiation to install the final substituent on the piperidine ring.

Scheme 4.37

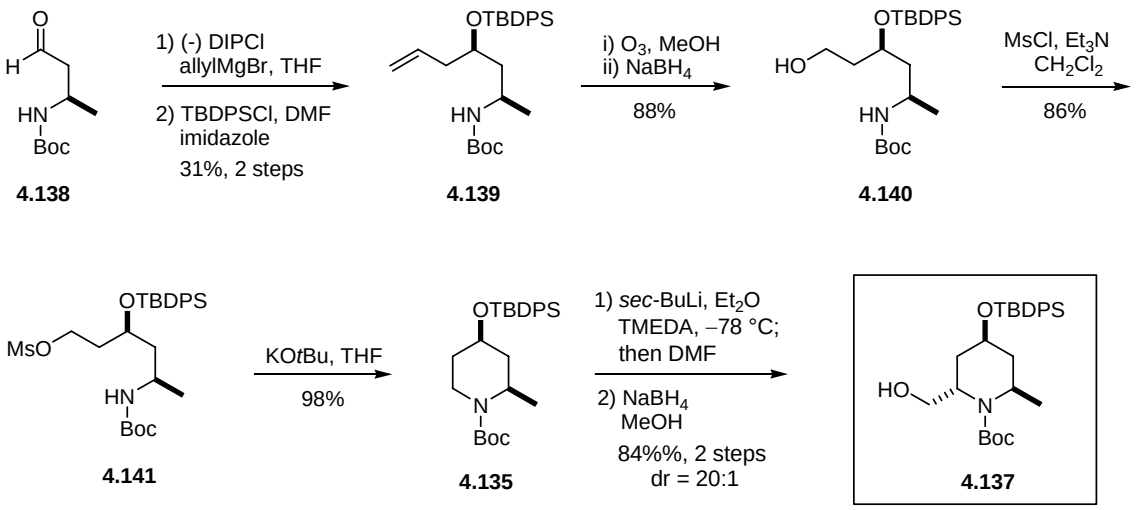


While the introduction of a methyl group via ortholithiation of **4.118** worked poorly (max 55%), the formylation of **4.135** proceeded in high yield and excellent diastereoselectivity. After some experimentation, the requisite aldehyde **4.136** could be obtained in 92% yield and in a diastereomeric ratio of approximately 20:1. Furthermore, the scale of the reaction was increased to 1.4 g without any reduction in yield or diastereoselectivity. With ample quantities of **4.136** in hand, the aldehyde function was then reduced to the primary alcohol **4.137** in 91% yield upon exposure of **4.136** to $NaBH_4$ (Scheme 4.37).

4.5.4 6-Exo-tet-cyclization/Beak Lithiation Approach: Successful Enantioselective Synthesis of the E-ring

After having developed a reliable approach to racemic **4.137**, it was necessary to adapt this route to afford enantiopure **4.137**. It was envisioned that the synthesis of the racemic material described above could be intersected if an enantioselective synthesis of **4.133** or **4.135** could be achieved. After some experimentation, success was eventually achieved using chemistry related to one of the early approaches to the piperidine E-ring. The synthesis started from aldehyde **4.138**, using an asymmetric Brown-allylation followed by protection of the secondary alcohol as its TBDPS-ether (Scheme 4.38). So far, **4.139** has been isolated in only 31% yield over the two steps, which is somewhat surprising given that the Cbz-protected derivative **4.90** underwent Brown allylation to afford the corresponding product in roughly 67% yield. Nevertheless, assuming that the yield can be improved upon further optimization, the synthesis was carried forward. Ozonolysis of the olefin in **4.139** followed by reductive workup with $NaBH_4$ delivered alcohol **4.140** in 88% yield. Following activation of the primary alcohol as the mesylation, the target piperidine **4.135** was obtained in excellent yield (98%) via 6-exo-tet ring-closure upon exposure of **4.141** to KO*t*Bu. From this point in the sequence, the chemistry was identical to that in the synthesis of racemic material (Scheme 4.38).

Scheme 4.38



Piperidine **4.137** has thus been prepared in enantiomerically pure form in seven steps from commercially available **4.138**. This compares favorably with Comins' methodology, which would have required two additional steps. Furthermore, employing Comins' strategy would also have required the four-step preparation of 8-phenylmenthyl chloroformate.

4.5.5 Attempted Preparation of the Organozinc Reagent

With trisubstituted piperidine **4.137** in hand, the next challenge involved the conversion of **4.137** to the corresponding iodide **4.100**, which would serve as the precursor for generating the organozinc reagent **4.6**. However, as observed in earlier approaches to this piperidine, upon attempted mesylation of the primary hydroxyl group of **4.137** in preparation for nucleophilic displacement of iodide, intramolecular ring-closure occurred to afford oxazolidinone **4.143** in 91% yield (Scheme 4.39). This material was a crystalline solid and was submitted for X-ray analysis to verify the stereochemical assignments. As expected, piperidine **4.143** had the requisite *S*,*S*,*R*-

configuration thus establishing the stereochemical outcome of the asymmetric Brown allylation as well as the Beak-lithiation.

Scheme 4.39

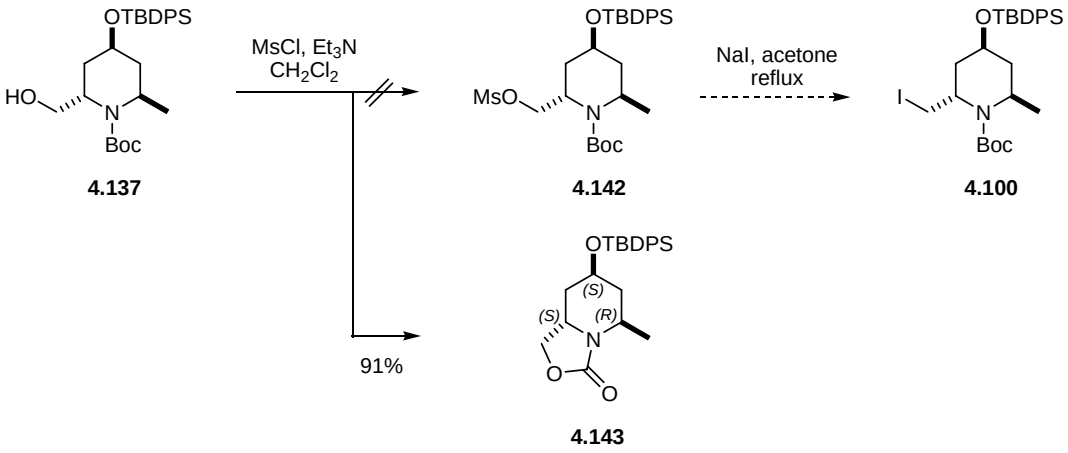
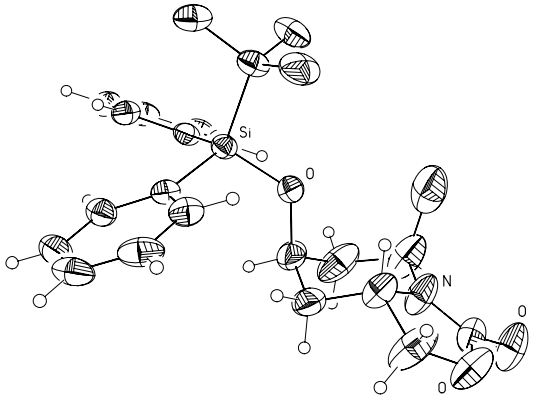


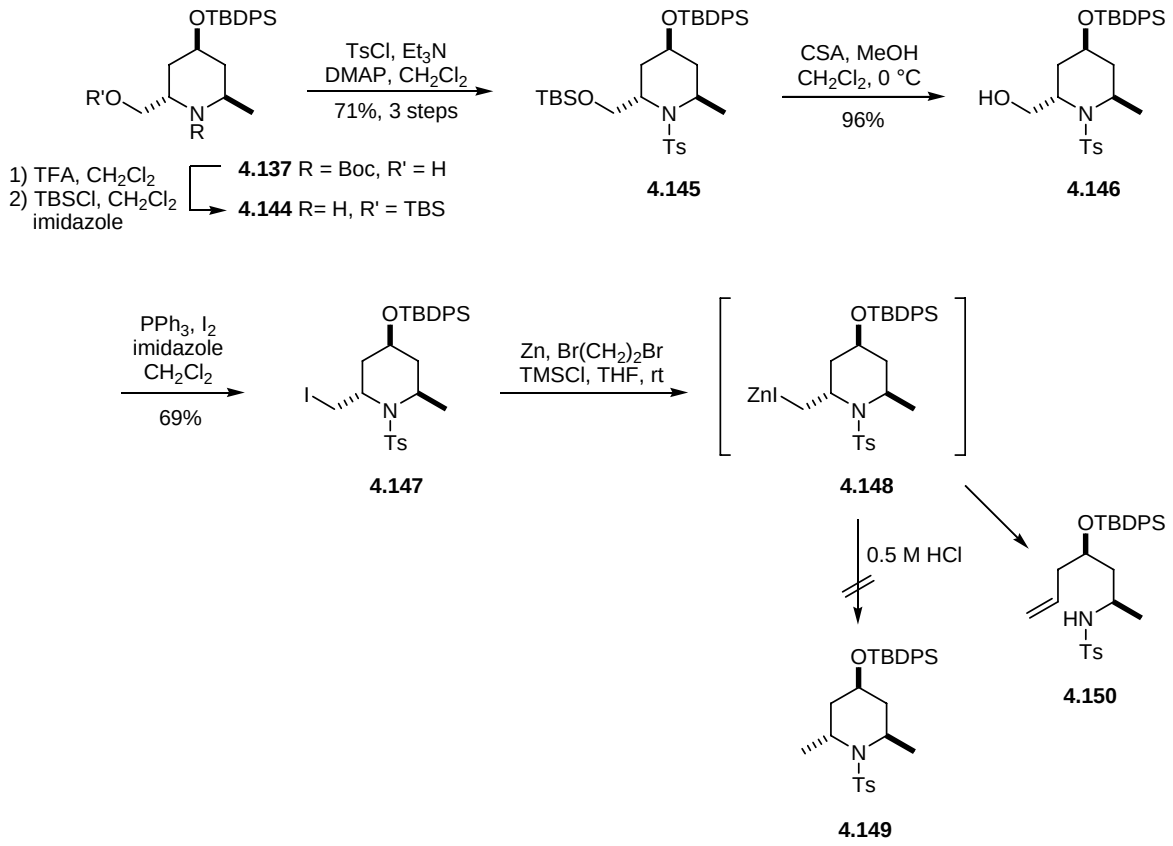
Figure 4.4 ORTEP plot of **4.143**. Displacement ellipsoids are scaled to the 50% probability level.



A possible solution to the problem of oxazolidinone formation was to use a different protecting group on the piperidine nitrogen. Toward this, end the corresponding sulfonamide **4.147** was prepared starting from **4.137**. TBS protection followed by tosylation of the piperidine nitrogen gave **4.145** in 72% yield over the two steps. The

TBS group was then removed in 96% yield setting the stage for the introduction of the requisite iodide. In the event, **4.146** was treated with PPh_3 and I_2 in the presence of imidazole to afford the iodide **4.147**, which could be isolated 69% yield. Before actually attempting the fragment coupling it was necessary to determine if the organozinc species **4.148** could indeed be generated from **4.147**. Following the conditions developed by Knochel and co-workers,[96] iodide **4.147** was treated with zinc dust that had been activated with $Br(CH_2)_2Br$ and TMSCl, to generate alkylzinc species **4.148**. In order to establish whether or not **4.148** had indeed been formed, the reaction was quenched with dilute acid. Unfortunately, none of the expected 2,6-dimethylpiperidine **4.149** was obtained. Instead, the acyclic material **4.150** resulting from β-elimination of the alkyl zinc species **4.148** was observed (Scheme 4.40). The reaction proceeded quickly at room temperature and had gone to completion in less than an hour as determined by ^1H NMR analysis of the crude reaction mixture. While this approach has been unsuccessful thus far, it may be worth re-examining at lower temperature. By using Riekie zinck, it may be possible to carry out the zinc insertion at low temperature at which β-elimination may be avoided

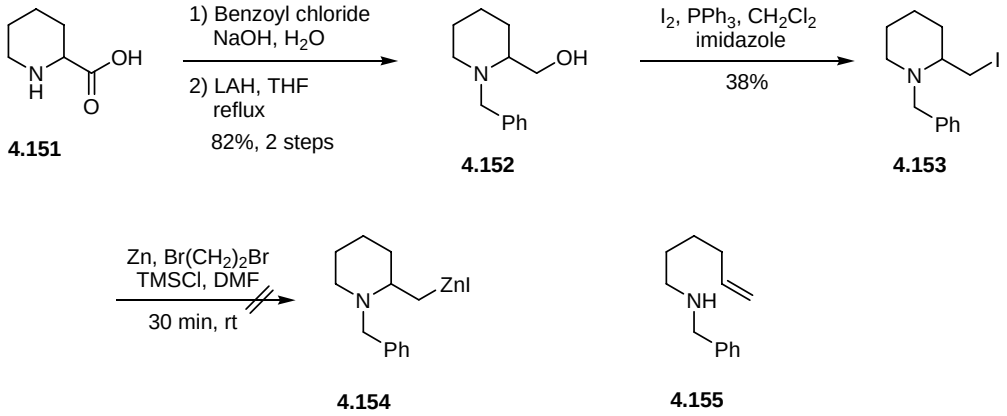
Scheme 4.40



While protecting the piperidine nitrogen as a sulfonamide avoided the problem of oxazolidinone formation, this protecting group was too electron withdrawing and favored β-elimination during the formation of the organozinc species. To address this new problem it was envisioned that the nitrogen could be protected with a benzyl group. We reasoned that β-elimination would be less likely with the nitrogen protected as a tertiary amine since the leaving group would be a negatively charged secondary amine. To test this hypothesis, a model system was devised as depicted in Scheme 4.41. The requisite iodide **4.153** was readily prepared from **4.52**, which was available in two steps from commercially available pipecolinic acid **4.151** as described in the literature.[156] The iodide

was then subjected to the Knochel procedure for direct insertion of zinc.[96] While THF is the most commonly used solvent for this transformation, DMF was used instead because it is known to coordinate more strongly to the organozinc species than does THF.[157] In spite of these efforts, β-elimination was again observed, and the olefin **4.155** was found to be the exclusive product as determined by ^{1}H NMR of the crude reaction mixture. It is perhaps not too surprising when considering that the alkyl zinc species could potentially coordinate with the tertiary nitrogen to render it a quaternary ammonium ion, which would be a good leaving group.

Scheme 4.41

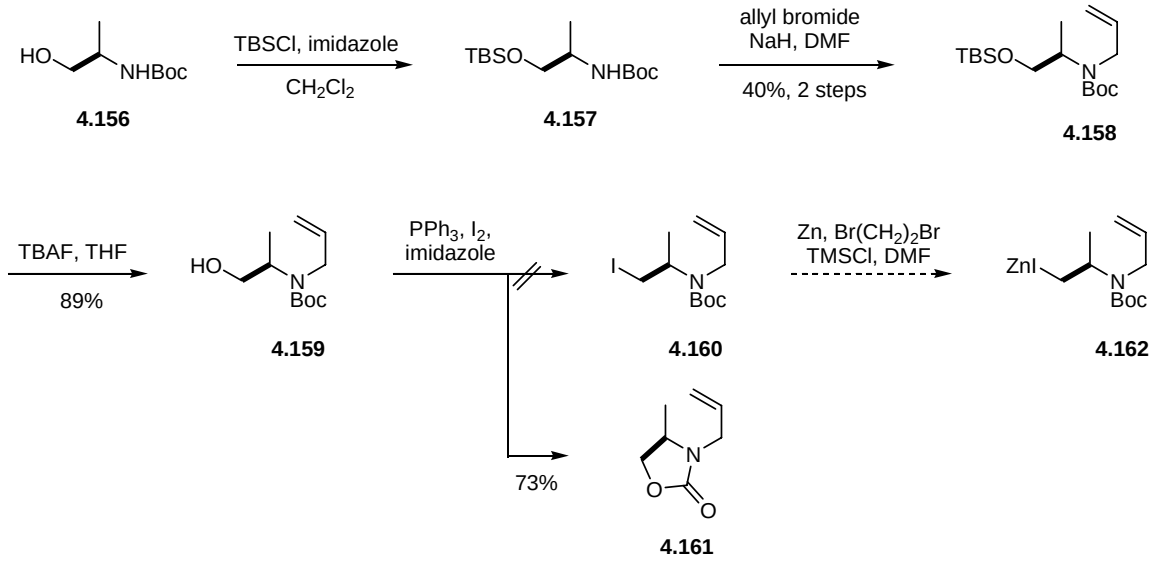


In a final attempt to realize the organozinc cross coupling approach, the Boc-protecting group was revisited since both the sulfonamide and benzyl protecting groups resulted in β-elimination following direct insertion of zinc. Jackson has described numerous examples of zincates derived from alkyl iodides bearing a *tert*-butyl carbamate in the β-position with no mention of oxazolidinone formation.[158] However, in all of these cases the substrates were acyclic. We therefore hypothesized that the high propensity for oxazolidinone formation that was observed in the piperidine substrates may be due to the presence of the 6-membered ring. As such, this problem could potentially be avoided if

an acyclic fragment was used instead. After successfully forming the organozinc species and effecting the cross coupling, the requisite piperidine may be formed by a cyclization event, perhaps by RCM. To examine the feasibility of this idea a model system was devised (Scheme 4.42).

The synthesis commenced with TBS-protection of Boc alaninol (**4.156**), followed by alkylation with allylbromide to give **4.158**. The silyl protecting group was removed to afford alcohol **4.159**, and this material was then subjected to the same conditions to generate the iodide as reported by Jackson.[158] However, contrary to expectations the oxazolidinone was again observed as the sole product of the reaction. This result stands in stark contrast to the results reported by Jackson.

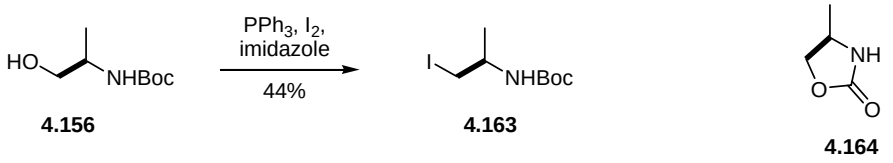
Scheme 4.42



The major difference between **4.160** and the majority of iodides described by Jackson is the presence of two alkyl groups on the carbamate nitrogen atom of **4.160** as apposed to a free NH. Hence, we hypothesized that oxazolidinone formation might be avoided if a mono substituted carbamate was used instead. To test this hypothesis we

attempted the conversion of Boc-alaninol (**4.156**) to iodide **4.163** (Scheme 4.43). Interestingly, this reaction did indeed afford the iodide albeit in only 44% yield, however, the ^{1}H NMR spectrum of the crude reaction mixture indicated a mixture (2:1) of iodide to oxazolidinone **4.164**. Although, one can envision a path forward in which a simple acyclic fragment derived from alanine is used in the cross coupling followed by construction of the piperidine ring, we opted not to pursue this route in favor of alternative, more convergent approaches (*vide infra*)

Scheme 4.43



4.156 **4.163** **4.164**

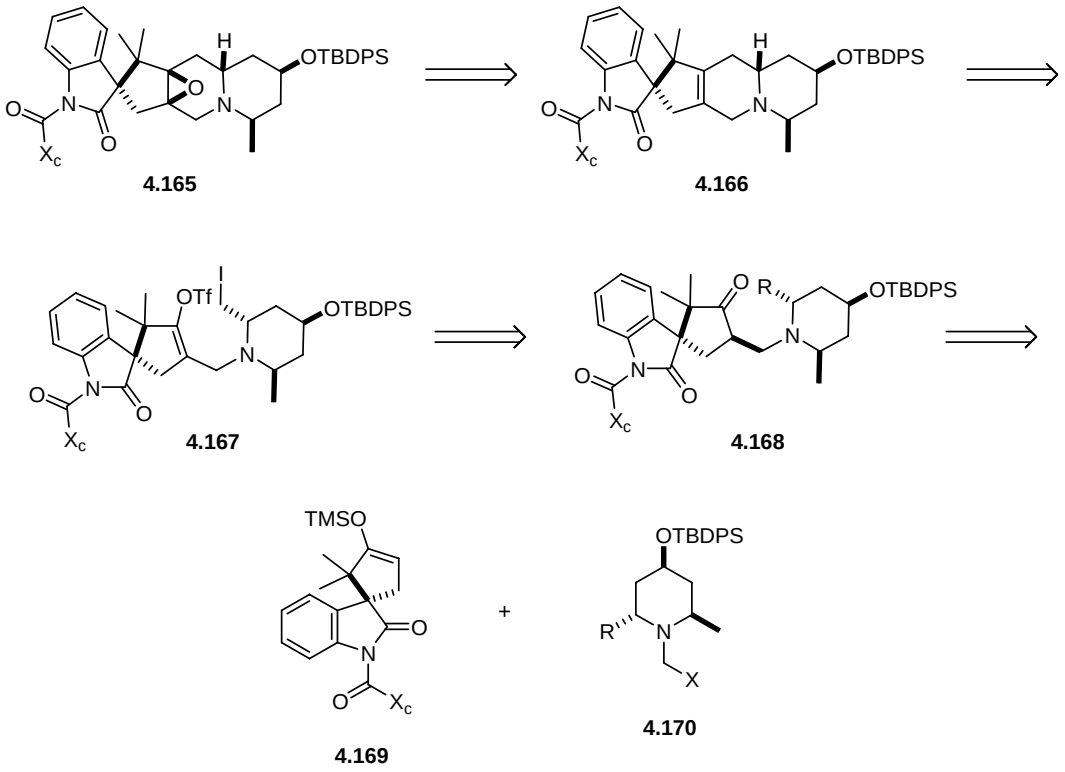
4.6 FRAGMENT COUPLINGS

4.6.1 Fragment Coupling via Mannich Reaction

Given the difficulties in preparing a suitable iodide and the corresponding organozinc species, attention was shifted in favor of alternative coupling strategies. As outlined in Scheme 4.44, **4.165** could be envisioned as coming from **4.166** via epoxidation with DMDO from the less sterically hindered face of the olefin. The tertiary amine in **4.66** would be protected in situ if necessary as the HCl salt or as an amine-borane complex.[159] The pentacyclic intermediate **4.166** was projected to arise from an intramolecular ring-closure of an alkyl samarium species, which could undergo addition/elimination to the triflate.[160] Triflate **4.167** would be obtained via standard functional group transformations from **4.168**, which in turn would be the product of the key fragment coupling of silyl enol ether **4.169** with iminium ion precursor **4.170** using a

Mannich reaction. Enders has shown that trimethylsilyl enol ethers undergo Mannich reaction with *N,O*-acetals in the presence of $BF_3 \cdot OEt_2$ in high yields;[161] however, Mannich reactions of silyl enol ethers with preformed iminium ions is a relatively young field, and not much work has been done in this area.[162]

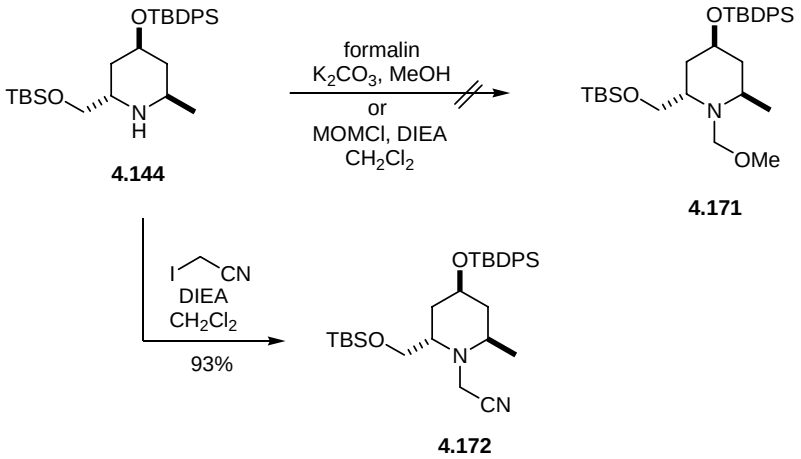
Scheme 4.44



In preparation for the fragment coupling, piperidine **4.144** needed to be converted to a suitable iminium ion precursor. Several attempts were made to generate the *N*,*O*-acetal **4.171**, but to no avail. The use of an α-aminonitrile appeared to be a good alternative since α-aminonitriles are known to readily ionize to give the corresponding iminium ion upon exposure to AgOTf. Thus, piperidine, **4.144** was treated with iodoacetonitrile and Hünigs' base to afford **4.172** in 93% yield (Scheme 4.45). These experiments were carried out using racemic **4.144** since the enantioselective route to

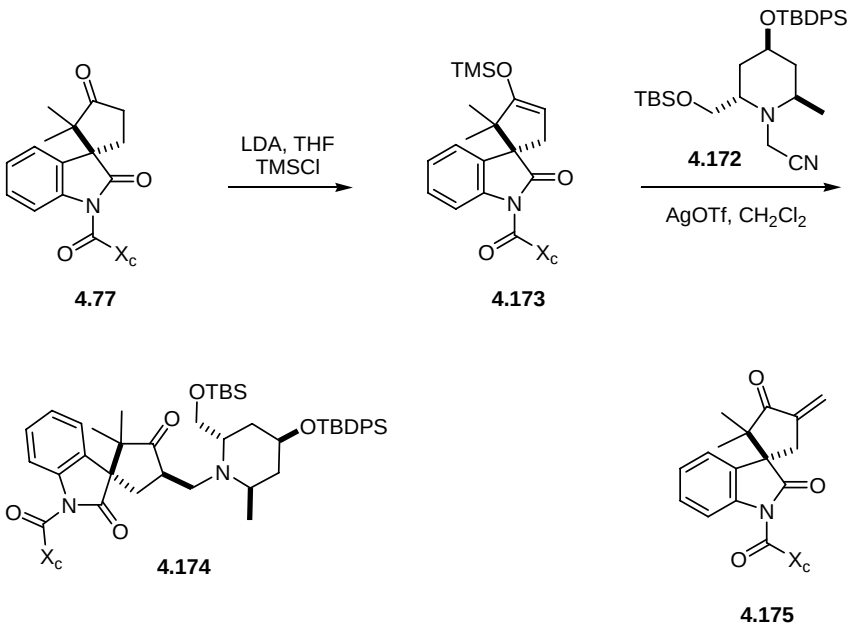
4.144 had not yet been developed at the time of these studies. With the key fragments in hand, the stage was then set for the pivotal Mannich reaction.

Scheme 4.45



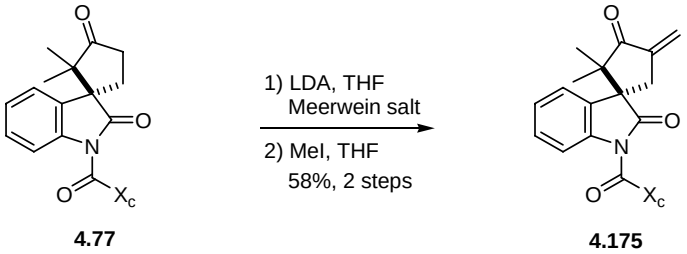
Deprotonation of **4.77** with LDA followed by the addition of TMSCl delivered the trimethylsilylenol ether **4.173**, which was submitted without further purification to the proposed fragment coupling (Scheme 4.46). Thus, silyl enol ether **4.173** and α-aminonitrile **4.172** were stirred in the presence of silver triflate to afford the advance tetracyclic intermediate **4.174** in about 54% yield over two steps. However, a disadvantage to this strategy quickly became apparent as the Mannich base **4.174** was rather unstable even to mildly acid conditions. In fact, upon TLC analysis on silica, substantial degradation of **4.174** was observed to form exocyclic olefin **4.175** via a retro-Michael reaction.

Scheme 4.46



The structure of **4.175** was corroborated by independently preparing **4.175** from ketone **4.77** (Scheme 4.47). Because of the instability of **4.174** to acid, it was necessary to deactivate the silica gel with triethylamine, but even when this was done, some fragmentation was observed and the **4.175** could not be isolated cleanly. Because of theis problem, the strategy involving fragment coupling via Mannich reaction was abandoned in favor of alternative approach (*vide infra*).

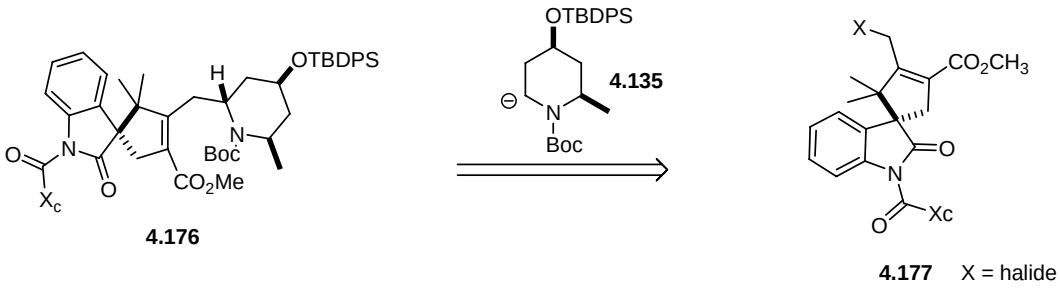
Scheme 4.47



4.6.2 Fragment Coupling via Lithiation/Alkylation

In parallel with the Mannich approach, an alternative coupling strategy was pursued. Since the Beak lithiation worked remarkably well in the synthesis of the piperidine fragment **4.137**, it was envisioned that one may be able to utilize this reaction to couple the two fragments of citrinadin A. As depicted in Scheme 4.48, we reasoned that tetracyclic intermediate **4.176** could be constructed by directed *ortho*-lithiation of piperidine **4.135** followed by alkylation with an allylhalide derivative of the spirocyclic fragment such as **4.177**.

Scheme 4.48



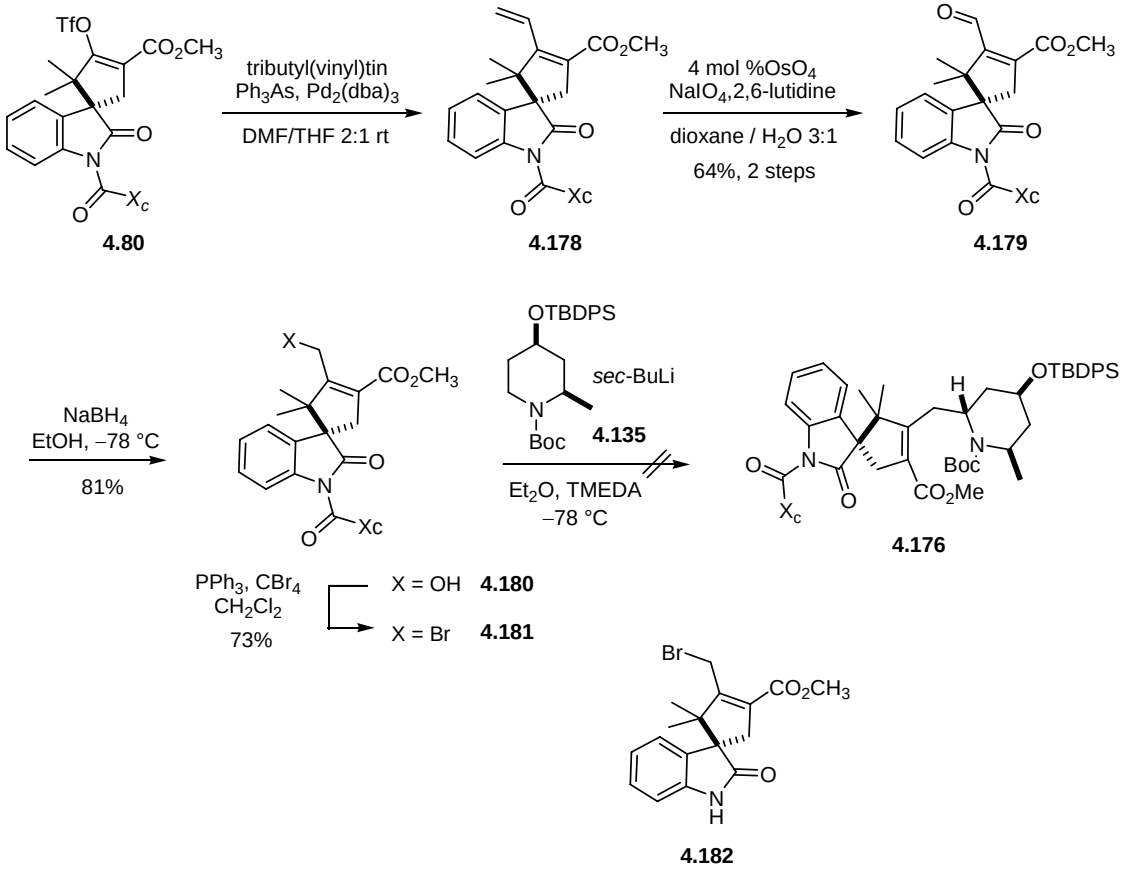
The synthesis of the allylhalide **4.177** commenced with a Stille-coupling of triflate **4.80** with tributylvinyl tin. In spite of the fact that the triflate is exceedingly hindered, the coupling proceeded smoothly at room temperature when using $Pd_2(dba)_3$ and Ph_3As as the catalyst system to afford **4.178** in good yield (Scheme 4.49). This was an important result in that it shows that **4.80** can undergo oxidative addition to palladium**,** and this may bode well for Pd-catalyzed couplings of more highly functionalized fragments in the future.

Enoate **4.178**, which was difficult to separate completely from the Ph_3As ligand, was subjected to a chemoselective Johnson-Lemieux cleavage of the more electron rich terminal olefin to give aldehyde **4.179** in 64% yield over the two steps. The next

transformation involved the reduction of the aldehyde function of **4.179** to give allylic alcohol **4.180**. It had been previously shown that the oxindole carbonyl group of **4.77**, which is part of an imide function because of the presence of the chiral auxiliary, is readily reduced to the corresponding aminal **4.78** when exposed to $NaBH_4$ at 0 °C (Scheme 4.49). To avoid this potential selectivity problem, the reduction was carried out at –78 °C in $EtOH/CH_2Cl_2$, conditions that are known to reduce aldehydes in the presence of a ketones.[163] Gratifyingly, when employing these conditions the desired allylic alcohol **4.180** could be isolated in 81% yield.

It now remained to convert the allylic alcohol **4.180** to a suitable halide. Toward this end the formation of the allyl iodide was attempted using I_2, PPh_3 and imidazole; however, while the reaction proceeded cleanly based on TLC analysis, the corresponding iodide was unstable to aqueous workup and silica gel chromatography and could only be isolated in diminished yields (<20%). On the other hand, the reaction of **4.180** with CBr_4 and PPh_3 proceeded smoothly to afford allyl bromide **4.181**, which in contrast to the iodide could be readily isolated in good yield (73%) (Scheme 4.49).

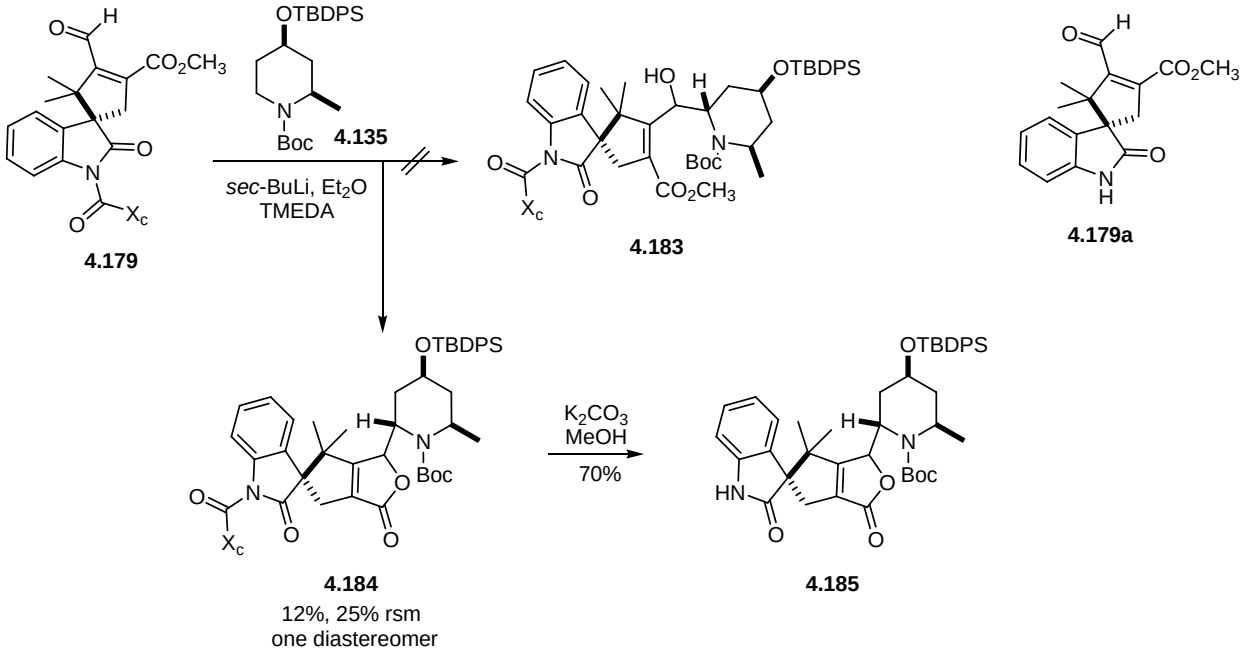
Scheme 4.49



With allyl bromide **4.181** in hand, the key coupling reaction was explored. Piperidine **4.135** was lithiated using the same conditions that were successfully utilized in the synthesis of piperidine **4.137**. Namely, exposure of **4.135** to *sec*-BuLi in the presence of TMEDA generated the corresponding lithiated species to which allylbromide **4.181** was added. Because no reaction was observed at low temperature, the cold bath was removed, and reaction was allowed to warm to room temperature. Unfortunately, none of the desired coupling product was obtained. Instead, allyl bromide **4.182** lacking the chiral auxiliary was isolated in about 48% yield. It appears that the electrophilic imide functionality is more susceptible toward attack of the lithiated piperidine than the allyl bromide.

A possible solution to this problem was to use aldehyde **4.179** since aldehydes have been reported to be better electrophiles than allyl halides in reactions with lithiated piperidines.[164] Preliminary experiments showed that this approach was indeed successful (Scheme 4.50). In the event, aldehyde **4.179** was added to the lithiated piperidine **4.135**, and the reaction was allowed to warm to room temperature to form adduct **4.184** in 12% yield along with 24% recovered aldehyde. Interestingly, the expected adduct **4.183** was not isolated, rather compound **4.184** in which the secondary alcohol had undergone ring-closure with the methyl ester to form a lactone was obtained. This product was isolated as a single diastereomer, although the configuration of the newly formed stereocenter was not determined. Lactone **4.184** was then subjected to K_2CO_3 in MeOH to effect the cleavage of the auxiliary and afford the advanced tetracyclic intermediate **4.185** in 70% yield.

Scheme 4.50

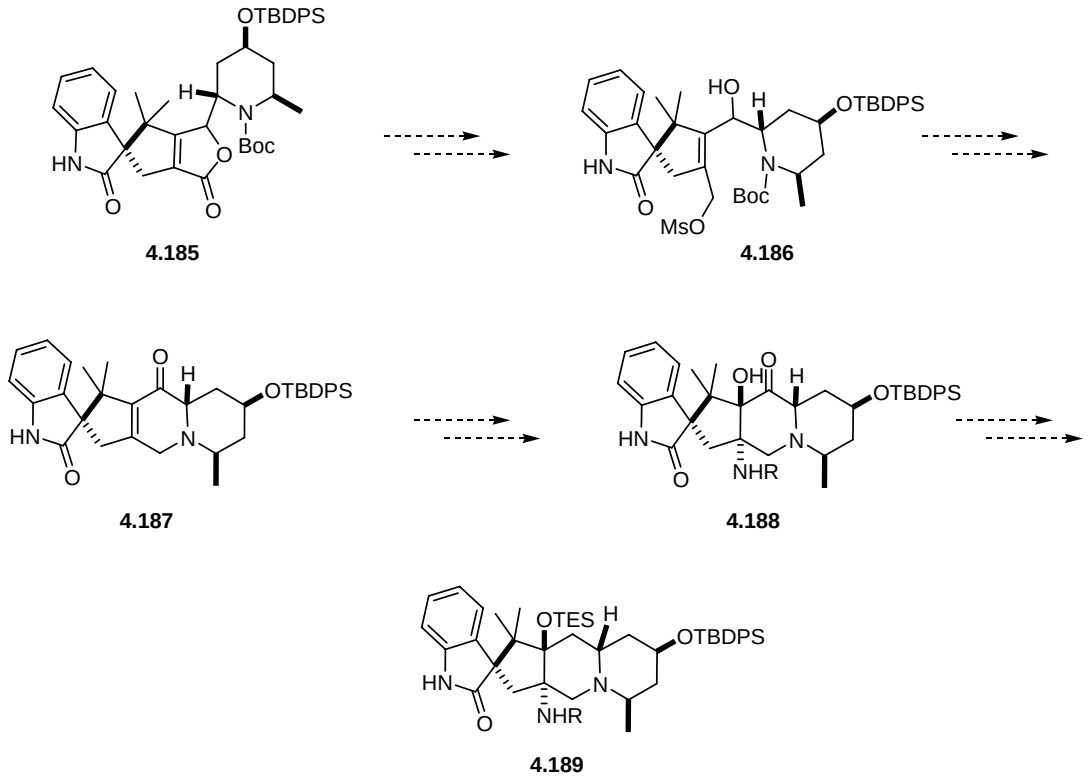


Several attempts were made to try to optimize the coupling reaction but to no avail. Again, it was determined that the lithiated piperidine preferentially attacks the imide functionality rather than the aldehyde as deprotected starting material **4.179a** was isolated in some of these reactions. A possible solution to this problem might involve removal of the auxiliary before performing the fragment coupling. An excess of lithiated piperidine or an exogenous base can then be used to deprotonated the oxindole NH prior to fragment coupling.

With a route to the tetracyclic intermediate **4.185** in place, one can envision a relatively straightforward path to complete the pentacyclic framework of citrinadin A. Reduction of the lactone function of **4.185** followed by selective mesylation of the primary alcohol would give **4.186**. Removal of the Boc group would result in

intermolecular alkylation to form the final D-ring, and oxidation of the secondary alcohol would furnish **4.187** (Scheme 4.51). The requisite amino and alcohol functionality on the five membered ring may then be installed via epoxidation from the least sterically hindered face of the enone with hydrogen peroxide followed by epoxide opening by an amine nucleophile. Following protection of the tertiary hydroxy in **4.188**, the carbonyl group would be removed via reduction to the secondary alcohol followed by Barton-McCombie deoxygenation.

Scheme 4.51

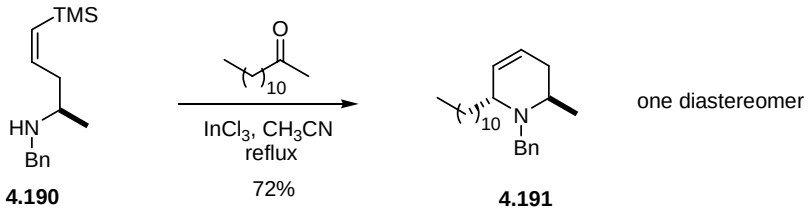


4.6.3 Attempted Fragment Coupling via Aldehyde/Vinylsilane Cyclization

While the synthesis of the advanced tetracyclic intermediate **4.185** represented an exciting and important milestone in the project, the need for a deoxygenation of ketone

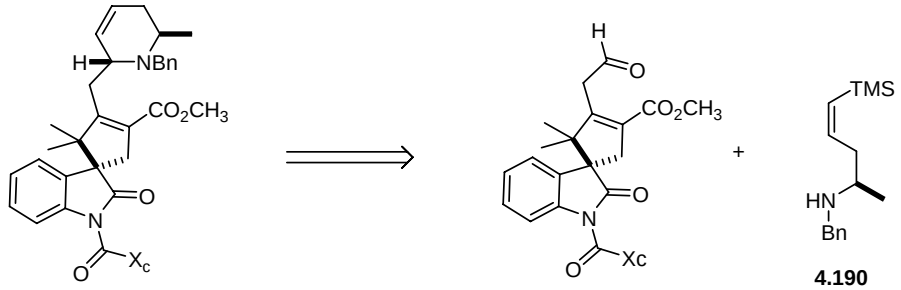
4.188 prompted us to investigate different strategy. Rather than attempting to couple a fully functionalized piperidine unit, we envisioned a stepwise approach in which triflate **4.80** would be coupled with a smaller fragment that could be elaborated into the requisite piperidine. Dobbs and co-workers have developed a convenient method for the synthesis of 2,6-*trans*-piperidines involving cyclization of a vinylsilane with an aldehyde using $InCl_3$ as the Lewis acid (Scheme 4.52).[165]

Scheme 4.52



This is an extension of work initially described by Overman and co-workers, who used protic acids to carry out the transformation and observed extensive racemization through an aza-Cope reaction.[166] On the contrary, using the mild Lewis acid catalyzed conditions described by Dobbs, racemization could be completely avoided. We felt that this chemistry could potentially be applied to the construction of the piperidine unit of citrinadin A as outlined in Scheme 4.53.

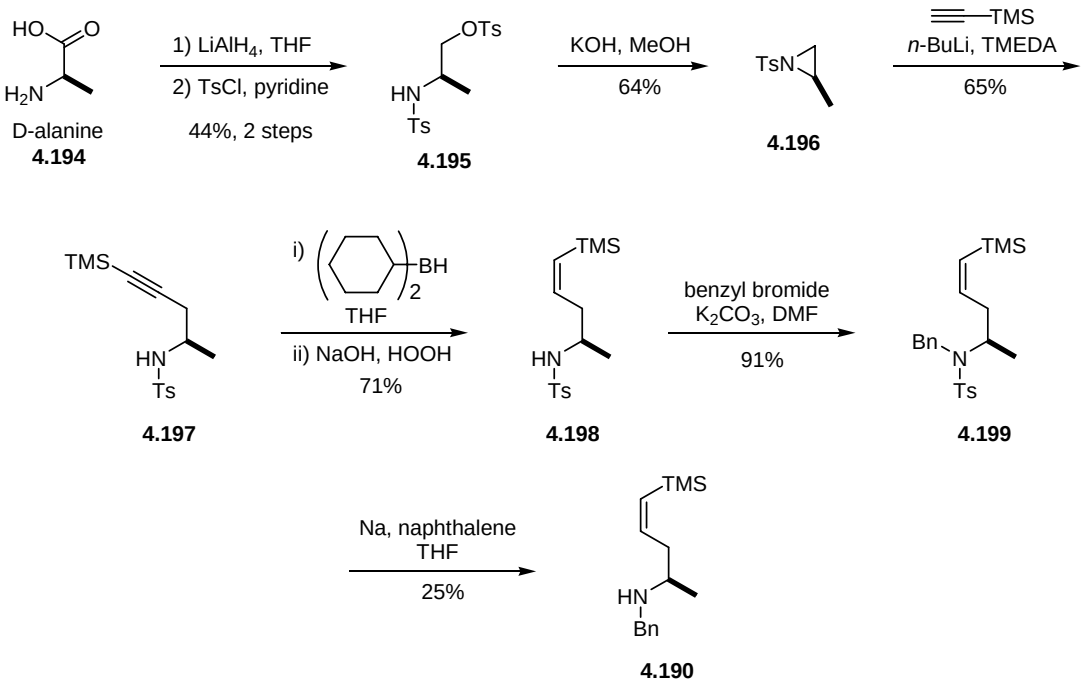
Scheme 4.53



The requisite enantiopure vinylsilane **4.190** was prepared according to the procedure by Overman (Scheme 4.54).[166] The synthesis commenced with the reduction of D-alanine (**4.194**) followed by tosylation of both the nitrogen and the primary hydroxyl group. Exposure of **4.195** to KOH/MeOH then resulted in intramolecular displacement of the tosylate to afford aziridine **4.196** in 64% yield. The aziridine was then subjected to ring-opening by lithium trimethylsilylacetylide to furnish alkyne **4.197**, which, in turn, was hydroborated with dicyclohexylborane, followed by protonolysis to afford vinylsilane **4.198** in 71% yield. At this point, all that remained was to replace the sulfonamide protecting group with a benzyl group. This was first attempted according to the procedure described by Overman in which the sulfonamide was treated with sodium naphthalenide.[166] While this procedure did afford some of the desired product as observed by ^{1}H NMR analysis of the crude reaction mixture, substantantial amounts of an unidentified side product were also formed. Additionally, the reaction was very slow. Mariano has described an improved method for the preparation of **4.190** in which **4.198** was first benzylated to give **4.199** followed by removal of the tosyl group by reduction using Na/Hg.[167] While the benzylation worked very well, the subsequent Na/Hg reduction only resulted in recovered starting material. Therefore, **4.199** was subjected to the original sodium naphthalenide procedure since it is known that tosyl groups can be

removed from benzylamines without affecting the benzyl group.[168] As shown in Scheme 4.54, the latter approach was successful and afforded sufficient quantities of vinylsilane **4.190** to test the key cyclization

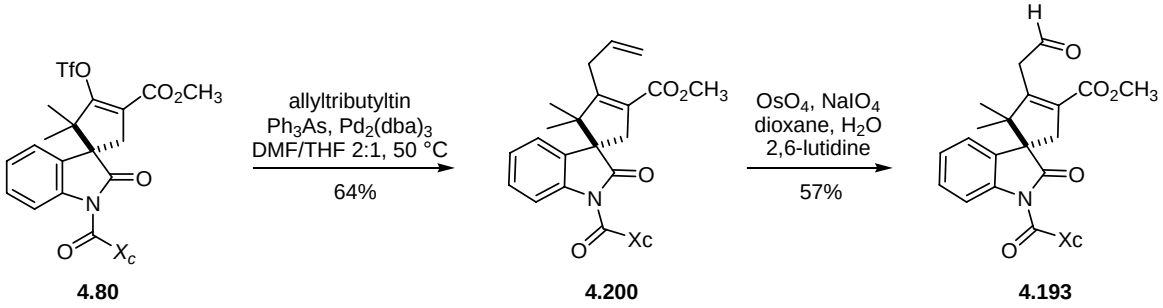
Scheme 4.54



A perhaps bigger challenge was the preparation of the requisite aldehyde coupling partner. After some experimentation we discovered that a strategy similar to that used for the synthesis of aldehyde **4.179** could be employed. This would involve a cross coupling of triflate **4.80** with an allyl group rather than and vinyl group. The requisite aldehyde **4.193** could then be accessed through a chemoselective oxidative cleavage of the terminal olefin (Scheme 4.55). A number of methods could be envisioned for the introduction of the allyl group. While Stille couplings of allylstannanes have been described in the literature, they are not very common.[169] However, since the Stille coupling of vinyltributyltin with the exceedingly hindered triflate **4.80** worked quite well, it was

worth examining if the analogous reaction using allyltributyltin would afford the desired product **4.200**. Gratifyingly, using identical conditions to those used for introducing the vinyl group resulted in the formation of **4.200** in 26% yield along with 20% recovered starting material. Perhaps the transmetalation step for the allylstannane is somewhat slower than that of the vinylstannane. Nevertheless, by heating the reaction to 50 °C overnight the reaction went to completion, and the allyl coupling product **4.200** could be isolated cleanly in 64% yield. Alternatively, one may be able to avoid the use of a stannane by performing a Negishi coupling using allyl zinc bromide. Finally, the requisite aldehyde **4.193** was obtained through cleavage of the terminal olefin via a Johnson-Lemieux oxidation that proceeded in 54% yield.

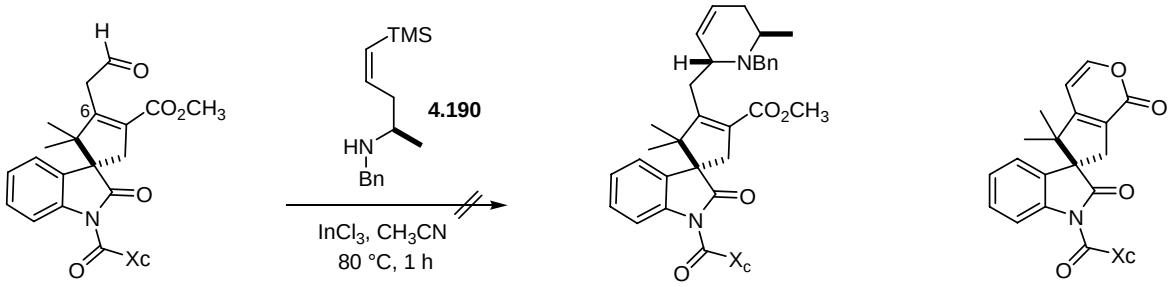
Scheme 4.55



4.80 **4.200** **4.193**

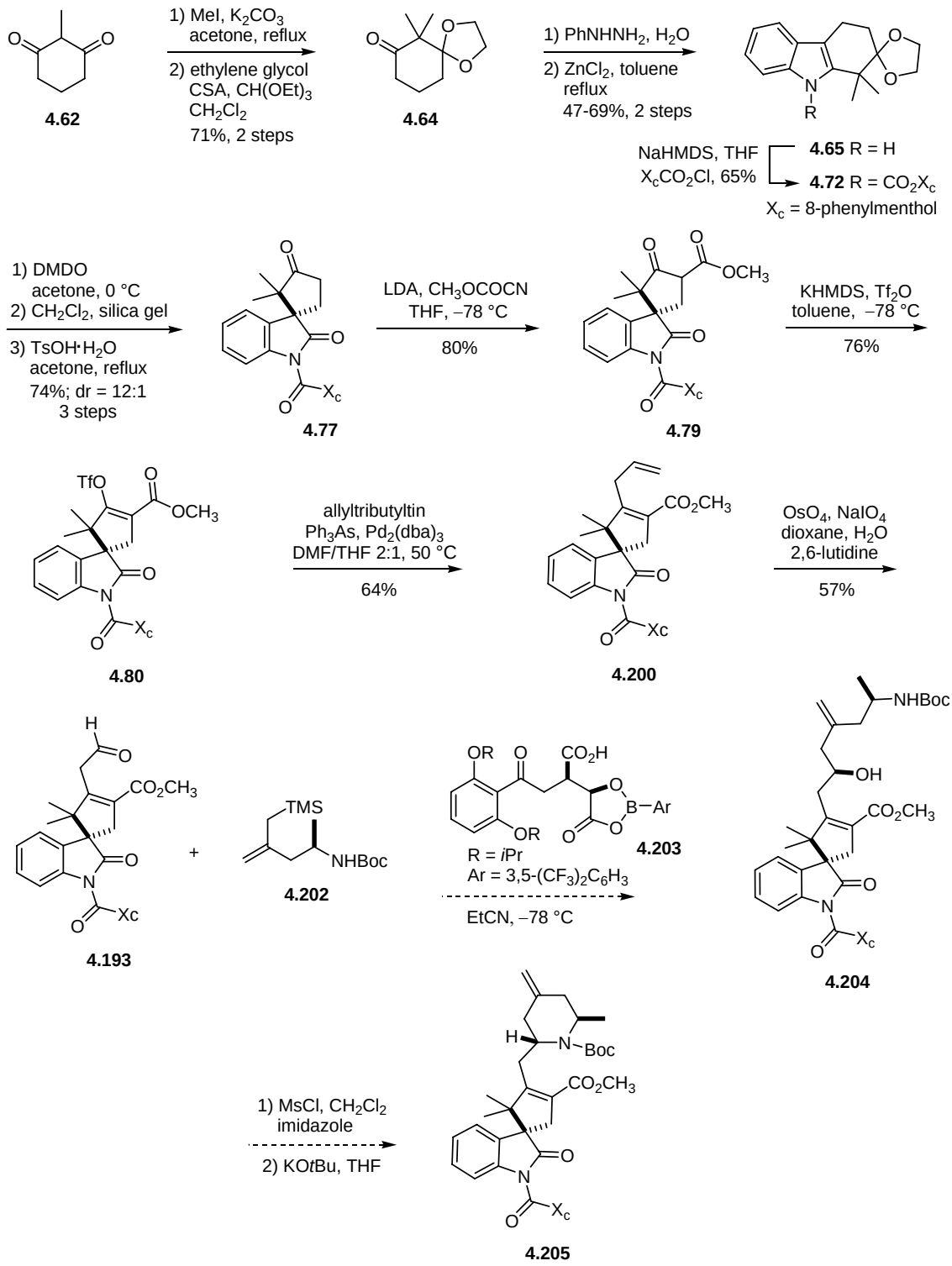
With both the vinylsilane **4.190** and the aldehyde coupling partner **4.193** in hand, the stage was set for the pivotal cyclization (Scheme 4.56). The vinylsilane was added to a solution of aldehyde **4.193** and $InCl_3$ in CH_3CN and stirred at 80 °C for 3 h. However, none of the desired product was observed. Rather lactone **4.201** was isolated in 43% yield as an inseparable mixture with unreacted vinylsilane.

Scheme 4.56



While the failure of the cyclization approach was disappointing, the achievement of an efficient synthesis of aldehyde **4.193** represents an important milestone in the project, especially since carbon-carbon bond formation at the highly hindered C(6) position can be performed. With this key intermediate in hand, the synthesis of which is summarized in Scheme 4.57, one can now focus on the various possibilities for advancing this material to install the piperidine unit. As depicted in Scheme 4.57, an attractive path forward would involve the Lewis acid catalyzed asymmetric addition of allylsilane **4.202** to aldehyde **4.193**, which unlike the cyclization can be carried out at –78 °C. Wender and co-workers utilized this reaction in their synthesis of 11-desmethyllaulimalide in which two complex fragments (both containing multiple stereocenters) were coupled in high yield and diastereoselectivity.[170] The requisite allyl silane **4.202** would be available simply through Boc-protection of the corresponding free amine which is a known compound.[171] Following successful fragment coupling, the resultant secondary alcohol in **4.204** would then be activated as the mesylate, which may undergo 6-exo-tet ring-closure upon exposure to KOtBu to form piperidine **4.205**.

Scheme 4.57


4.62
1) MeI, K2CO3 acetone, reflux
2) ethylene glycol CSA, CH(OEt)3 CH2Cl2 71%, 2 steps
4.64
1) PhNHNH2, H2O
2) ZnCl2, toluene reflux 47-69%, 2 steps
NaHMDS, THF XcCO2Cl, 65%
4.65 R = H
4.72 R = CO2Xc
Xc = 8-phenylmenthol
1) DMDO acetone, 0 °C
2) CH2Cl2, silica gel
3) TsOH·H2O acetone, reflux 74%; dr = 12:1 3 steps
4.77
LDA, CH3OCOCN THF, –78 °C
80%
4.79
KHMDS, Tf2O toluene, –78 °C
76%
4.80
allyltributyltin Ph3As, Pd2(dba)3 DMF/THF 2:1, 50 °C
64%
4.200
OsO4, NaIO4 dioxane, H2O 2,6-lutidine
57%
4.193
4.202
R = iPr
Ar = 3,5-(CF3)2C6H3
4.203
EtCN, –78 °C
4.204
1) MsCl, CH2Cl2 imidazole
2) KOtBu, THF
4.205

4.7 CONCLUSION

The presence of the highly functionalized spirooxindole motif in citrinadin A presents an opportunity to develop novel methods and synthetic strategy, since the existing methodologies for spirooxindole synthesis cannot be readily applied to the enantioselective synthesis of spirocyclic fragment **4.193**. A novel enantioselective oxidative rearrangement of a prochiral indole proceeded in 55-60% ee in a model system, but the utility of this tactic was limited in that the yield could not be increased above 20% using the citrinadin substrate. This was presumed to be due to steric hindrance of the indole C(2),C(3) double bond. Nevertheless, this approach may be of utility in simpler systems and therefore warrants further investigation.

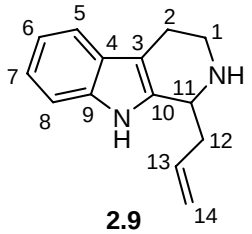
An alternative approach was developed involving a DMDO-mediated oxidative rearrangement using an 8-phenylmenthol-derived chiral auxiliary on the indole nitrogen. This transformation proceeds in 78% yield and excellent diastereomeric ratio (dr = 12:1) on gram scale, and the presence of a gem-dimethyl group was found to enhance diastereoselectivity relative to indoles lacking this functionality. There are a number of natural products that have a substitution pattern similar to that of citrinadin A,[87,88,89,90] and this approach may be applicable to their synthesis.

The utility of our spirooxindole synthesis was evidenced through a concise synthesis of the advanced intermediate **4.193** in only 12 steps and 6% overall yield. After successful carbon-carbon bond formation at the highly hindered C(6) position via a rarely used Stille coupling to introduce an allyl group, a clear path forward can be envisioned. This will involve the asymmetric addition of allyl silane **4.202** to afford intermediate **4.204**, which has all the requisite functionality in place to complete the pentacyclic

framework of citrinadin. Thus, the application of our DMDO-mediated oxidative rearrangement promises to allow for a concise enantioselective synthesis of citrinadin A.

Chapter 5: Experimental Section

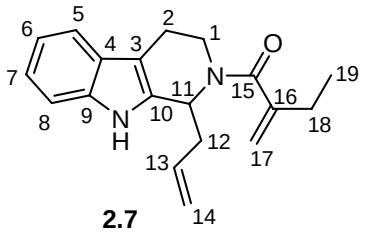
General Methods. Solvents and reagents were reagent grade and used without purification unless otherwise specified. CH_2Cl_2, *i*-Pr_2NH and Et_3N were freshly distilled from CaH_2. THF was passed through two columns of neutral alumina. DMF was passed through two columns of molecular sieves. Reactions involving air- of moisture-sensitive reagents or intermediates were performed under an inert atmosphere of argon or nitrogen in glassware that had been flame dried. Melting points are uncorrected. Infrared (IR) spectra were recorded neat on sodium chloride plates and are reported in wave numbers (cm^{-1}). ^1H and ^{13}C NMR spectra were obtained as solutions in $CDCl_3$ unless otherwise noted, and chemical shifts are reported in parts per million (ppm) downfield from $(CH_3)_4Si$ (TMS). Coupling constants are reported in hertz (Hz). Spectral splitting patterns are designated as follows: s, singlet; br, broad; d, doublet; t, triplet; q, quartet.



2.9

1-Allyl-2,3,4,9-tetrahydro-1*H*-β-carboline (2.9) (mp1-095). BF_3_OEt_2 (1.08 mL, 8.56 mmol) was added to a solution of 4,9-dihydro-3*H*-β-carboline **2.8** in THF (44 mL) cooled to –30 °C. The solution was stirred for 10 min, whereupon a 1.0 M solution of allyl magnesiumbromide in ether (1.0 M, 25.6 mL, 25.6 mmol) was added via addition funnel over 45 min. After the addition was complete, the stirring was continued at –30 °C for 2 h, whereupon saturated aqueous $NaHCO_3$ (10 mL) was added. The resulting slurry was poured into a separatory funnel containing saturated aqueaous $NaHCO_3$ (50

mL) and water (50 mL), and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with Et_3N/MeOH/CH_2Cl_2 (1:3:97) to give 1.52 g (81%) of **2.9** as a yellow solid. The ^1H NMR spectrum was identical to that previously reported in the literature.[59]

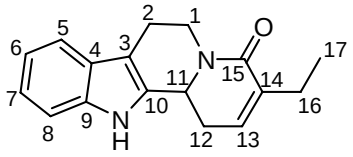


2.7

1-(1-Allyl-1,3,4,9-tetrahydro-β-carbolin-2-yl)-2-ethylpropenone (2.7) (mp1-101). A solution of **2.8** (100 mg, 0.42 mmol), 2-ethyl-acrylic acid (57 mg, 0.57 mmol), Et_3N (0.12 mL, 0.83 mmol), HOBT (113 mg, 0.83 mmol) and EDCI·HCl (88 mg, 0.46 mmol) in CH_2Cl_2 (4.2 mL) was stirred for 16 h at room temperature. The reaction was poured into EtOAc (20 mL) and the organic mixture was washed with 0.5 M aqueous HCl (2 × 10 mL), saturated aqueous $NaHCO_3$ (2 × 10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column-chromatography eluting with hexanes/EtOAc (1:3) to afford 105 mg (85%) of the title compound as white solid: mp 113-115 °C; ^{1}NMR (500 MHz) δ 8.33 (s, 1H), 7.45 (d, *J* = 7.8 Hz, 1 H), 7.31 (d, *J* = 8.0 Hz, 1 H), 7.18-7.12 (m, 1 H), 7.11-7.08 (m, 1 H), 6.01-5.91 (m, 1 H), 5.79 (t, *J* = 6.6 Hz, 1 H), 5.19 (s, 1 H), 5.14-5.10 (comp, 2 H), 5.07 (s, 1 H), 4.25-4.18 (m, 1 H), 3.51-3.41 (m, 1 H), 2.81-2.74 (comp, 2 H), 2.39 (q, *J* = 7.3 Hz, 2 H), 1.11 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (500 MHz) δ 171.8, 146.8, 136.1, 134.4, 133.6, 126.5, 121.9, 119.5, 118.4, 118.0, 112.6, 111.1, 107.7, 48.35, 41.86, 39.1, 27.3, 22.3, 11.7; IR (neat) 3258, 2962, 2906, 1601, 1470, 1442, 1300, 1180,

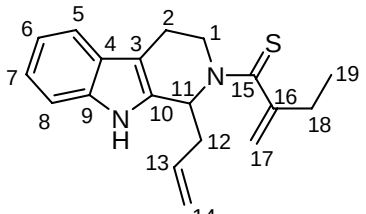
913, 741 cm^{-1}; mass spectrum (CI) *m/z* 295.1807 [$C_{19}H_{22}N_2O$ (M+1) requires 295.1810], 253, 295 (base), 323, 335, 377.

NMR Assignments. ^{1}NMR (500 MHz) δ 8.33 (s, 1H, NH), 7.45 (d, *J* = 7.8 Hz, 1 H, C5-H), 7.31 (d, *J* = 8.0 Hz, 1 H, C8-H), 7.18-7.12 (m, 1 H, C7-H), 7.11-7.08 (m, 1 H, C6-H), 6.01-5.91 (m, 1 H, C13-H), 5.79 (t, *J* = 6.6 Hz, 1 H, C11-H), 5.19 (s, 1 H, C17-H), 5.14-5.10 (comp, 2 H, C14-H), 5.07 (s, 1 H, C17-H), 4.25-4.18 (m, 1 H, C2-H), 3.51-3.41 (m, 1 H, C2-H), 2.81-2.74 (comp, 2 H, C1), 2.39 (q, *J* = 7.3 Hz, 2 H, C18-H), 1.11 (t, *J* = 7.3 Hz, 3 H, C19-H); ^{13}C NMR (500 MHz) δ 171.8 (C15), 146.8 (C16), 136.1 (C9), 134.4 (C13), 133.6 (C4), 126.5 (C10), 121.9 (C7), 119.5 (C6), 118.4 (C14), 118.0 (C5), 112.6 (C17), 111.1 (C8), 107.7 (C3), 48.35 (C11), 41.86 (C2), 39.1 (C14), 27.3 (C18), 22.3 (C1), 11.7 (C19).



2.6

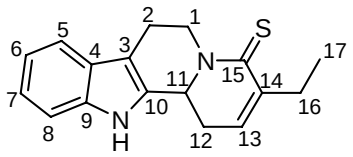
3-Ethyl-6,7,12,12b-tetrahydro-1*H*-indolo[2,3-*a*]quinolizin-4-one (2.6) (mp1-103). A solution of **2.7** (21 mg, 0.07 mmol) and Grubbs' second-generation catalyst (9.1 mg, 0.01 mmol) in degassed CH_2Cl_2 (3.55 mL) was stirred at 45 °C under argon for 16 h. The mixture was cooled to room temperature, DMSO (40 μL, 0.564 mmol) was added, and the mixture was stirred for 16 h. The reaction was concentrated under reduced pressure, and the residue was purified by flash column-chromatography MeOH/CH_2Cl_2 (0.5:99.5) to give 16 mg (87%) of **2.6** as a clear colorless glass. The ^{1}H NMR spectrum was identical to that previously reported in the literature.[58]



2.13

1-(1-Allyl-1,3,4,9-tetrahydro-β-carbolin-2-yl)-2-ethylpropenethione (2.13) (mp1-120). A solution of **2.7** (300 mg, 1.02 mmol) in THF (19.5 mL) was added via cannula to a refluxing solution of Lawesson's reagent (491 mg, 1.22 mmol) in THF (24 mL). The reaction was heated under reflux for 3 h, whereupon additional Lawesson's reagent (250 mg, 0.51 mmol) was added. After refluxing for 2 h, the reaction was concentrated under reduced pressure. The residue was dissolved in water (50 mL) and brine (10 mL), and the aqueous mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (1:1, then 1:5) to give 338 mg (86%) of **2.13** as a pale yellow solid: mp 133-135 °C; ^{1}NMR (500 MHz, DMSO-d_6) δ 10.68 (s, 1H), 7.40 (d, J = 7.8 Hz, 1 H), 7.34 (d, J = 8.1 Hz, 1 H), 7.09-7.05 (m, 1H), 7.01-6.94 (m, 1 H), 6.86-6.79 (m, 1 H), 6.01-5.90 (m, 1 H), 5.19-5.02 (comp, 2 H), 4.97 (s, 1 H), 4.82 (s, 1 H), 4.50 (app dd, J = 13.0, 4.5 Hz, 1 H), 3.70 (app td, J = 13.0, 4.2 Hz, 1 H), 2.99-2.90 (m, 1 H), 2.88-2.71 (comp, 3 H), 2.40 (q, J = 7.2 Hz, 2 H), 1.10 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (500 MHz) δ 201.6, 151.9, 136.0, 133.4, 132.5, 125.7, 120.7, 118.2, 117.2, 110.7, 108.5, 105.8, 53.7, 45.6, 37.5, 28.0, 21.6, 11.0; IR (neat)3393, 3266, 2971, 2907, 1468, 1431, 1252, 1231, 917, 745 cm^{-1}; mass spectrum (CI) *m/z* 311.1582 [$C_{19}H_{22}N_2S$ (M+1) requires 311.1582], 277, 311 (base), 313, 339, 351.

NMR Assignments. ^{1}NMR (500 MHz, DMSO-d_6) δ 10.68 (s, 1H, NH), 7.40 (d, *J* = 7.8 Hz, 1 H, C5-H), 7.34 (d, *J* = 8.1 Hz, 1 H, C8-H), 7.09-7.05 (m, 1H, C7-H), 7.01-6.94 (m, 1 H, C6-H), 6.86-6.79 (m, 1 H, C13-H), 6.01-5.90 (m, 1 H, C11-H), 5.19-5.02 (comp, 2 H, C14-H), 4.97 (s, 1 H, C17-H), 4.82 (s, 1 H, C17-H), 4.50 (app dd, *J* = 13.0, 4.5 Hz, 1 H, C2-H), 3.70 (app td, *J* = 13.0, 4.2 Hz, 1 H, C2-H), 2.99-2.90 (m, 1 H, C1-H), 2.88-2.71 (comp, 3 H, C1-H & C12-H), 2.40 (q, *J* = 7.2 Hz, 2 H, C18-H), 1.10 (t, *J* = 7.2 Hz, 3 H, C19-H); ^{13}C NMR (500 MHz) δ 201.6 (C15), 151.9 (C16), 136.0 (C9), 133.4 (C13), 132.5 (C4), 125.7 (C10), 120.7 (C7), 118.2 (C6), 117.2 (C5 & C14), 110.7 (C8), 108.5 (C17), 105.8 (C3), 53.7 (C11), 45.6 (C2), 37.5 (C1), 28.0 (C18), 21.6 (C12), 11.0 (C19).

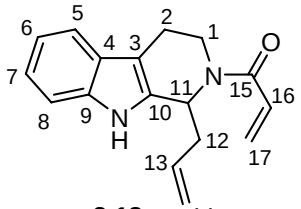


2.14

3-Ethyl-6,7,12,12b-tetrahydro-1*H*-indolo[2,3-*a*]quinolizine-4-thione (2.14) (mp1-126). A solution of **2.13** (22 mg, 0.07 mmol) and Grubbs' second-generation catalyst (9 mg, 0.01 mmol) in degassed dichloroethane (3.55 mL) was stirred at 65 °C under argon for 3 h. The mixture was cooled to room temperature, DMSO (30 μL, 0.42 mmol) was added, and the mixture was stirred at room temperature for 16 h. The reaction was concentrated under reduced pressure, and the residue was purified by flash chromatography hexanes/EtOAc (4:1) to give 4.5 mg (21%) of recovered starting material **27** and 9 mg (45%) of **28** as an orange solid: mp 141-145 °C; ^{1}NMR (500 MHz) δ 7.86 (s, 1 H), 7.54 (d, *J* = 7.8 Hz, 1 H), 7.33 (d, *J* = 8.0 Hz, 1 H), 7.20-7.17 (m, 1 H), 7.15-7.12 (m, 1 H), 6.27-6.22 (m, 2 H), 4.70 (dd, *J* = 14.5, 4.4 Hz, 1 H), 3.22-3.19 (m, 1

H), 2.98-2.92 (m, 2 H), 2.73-2.67 (m, 3 H), 2.35 (app tq, *J* = 14.5, 2.4 Hz, 1 H), 1.11 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (500 MHz) δ 194.6, 142.1, 136.6, 132.2, 126.3, 124.5, 122.5, 120.1, 118.6, 111.0, 109.9, 53.3, 47.6, 31.1, 28.4, 20.8, 13.1; IR (neat) 3278, 2923, 1606, 1417, 1308, 1193, 1056, 746 cm^{-1}; mass spectrum (CI) *m/z* 283.1262 [$C_{17}H_{18}N_2S$ (M+1) requires 283.1269], 249, 283 (base), 297, 311, 339.

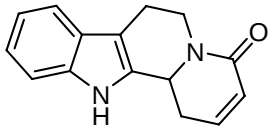
NMR Assignments. ^{1}NMR (500 MHz) δ 7.86 (s, 1 H, NH), 7.54 (d, *J* = 7.8 Hz, 1 H, C5-H), 7.33 (d, *J* = 8.0 Hz, 1 H, C8-H), 7.20-7.17 (m, 1 H, C7-H), 7.15-7.12 (m, 1 H, C6-H), 6.27-6.22 (m, 2 H, C2-H & C13-H), 4.70 (dd, *J* = 14.5, 4.4 Hz, 1 H, C11-H), 3.22-3.19 (m, 1 H, C2-H), 2.98-2.92 (m, 2 H, C1-H), 2.73-2.67 (m, 3 H, C12-H & C16-H), 2.35 (app tq, *J* = 14.5, 2.4 Hz, 1 H, C12-H), 1.11 (t, *J* = 7.4 Hz, 3 H, C17-H); ^{13}C NMR (500 MHz) δ 194.6 (C15), 142.1 (C9), 136.6 (C4), 132.2 (C10), 126.3 (C13), 124.5 (C14), 122.5 (C7), 120.1 (C6), 118.6 (C5), 111.0 (C8), 109.9 (C3), 53.3 (C11), 47.6 (C2), 31.1 (C12), 28.4 (C16), 20.8 (C1), 13.1 (C17).



2.18

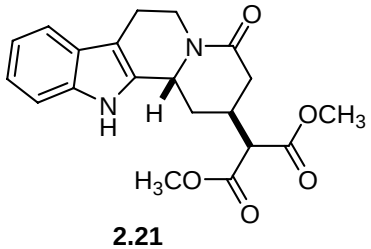
1-(1-Allyl-1,3,4,9,tetrahydro-β-carbolin-2-yl)-propenone (2.18) (mp1-149). Acryloyl chloride (485 mg, 435 μL, 5.36 mmol) was added to a mixture of **2.8** (1.00 g, 5.88 mmol) and allyltributyltin (1.62 g, 1.51 mL, 4.88 mmol) in CH_2Cl_2 (60 mL) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C and 12 h at room temperature. The volatiles were evaporated under reduced pressure and the residue was purified by flash column-chromatography on silica gel, eluting with EtOAc/hexanes (1:2–2:3) to give 980

mg (75%) of **2.18** as a colorless oil. The ^{1}H and ^{13}C NMR spectra are consistent with those previously reported for **2.18**.[45]



2.17

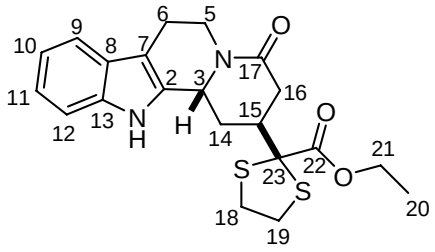
6,7,12,12b-Tetrahydro-1*H*-indolo[2,3-*a*]quinolizin-4-one (2.17) (mp2-030). Grubbs' first-generation catalyst (462 mg, 0.561 mmol, 4 mol%) was added to a solution of **2.18** (3.73 g, 14.0 mmol) in CH_2Cl_2 (610 mL) at room temperature. The reaction mixture was stirred for 15 h, whereupon dimethylsulfoxide (2.00 mL, 2.20 g, 28.1 mmol) was added and the reaction was stirred at room temperature over night. The solvent was removed under reduced pressure, EtOAc (10 mL) was added, and the mixture was cooled to 4 ˚C over night. The crude solid was triturated with EtOAc and recrystallized from CH_2Cl_2/$CHCl_3$, and the mother liquors were purified by flash column-chromatography on silica gel, eluting with EtOAc to afford a total of 2.91 g (87%) of **2.17** as a pale grey solid. mp = 228-229 °C (CH_2Cl_2), Lit.[67] 229-231 °C. The ^{1}H and ^{13}C NMR spectra are consistent with those previously reported for **2.17**.[45]



2.21

2-(4-Oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-2-yl)malonic acid dimethyl ester (2.21) (mp2-166). Dimethyl malonate (0.29 mL, 2.51 mmol) was added to a suspension of NaH (60% suspension in mineral oil, 30 mg, 1.25 mmol) in

THF (15 mL) and stirred for 5 min. Solid **2.17** (60 mg, 0.25 mmol) was added and the solution was heated under reflux for 48 h. The reaction mixture was cooled to room temperature and a saturated aqueous solution of $NaHCO_3$ (0.3 mL) and EtOAc (10 mL) was added. Stirring was continued for 15 min, the mixture was dried ($MgSO_4$) and the volatiles were removed under reduced pressure. The crude product was purified by flash column-chromatography on silica gel, eluting with EtOAc to give 68 mg (74%, *dr* = 60:40) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of diastereomers) δ 8.72 (br s, 0.6 H), 8.64 (br s, 0.4 H), 7.48 (d, *J* = 7.5 Hz, 0.6 H), 7.46 (d, *J* = 7.5 Hz, 0.4 H), 7.36 (d, *J* = 7.5 Hz, 0.4 H), 7.29 (d, *J* = 7.8 Hz, 0.6 H), 7.19-7.06 (comp, 2 H), 5.18-5.10 (m, 0.6 H), 5.04-4.99 (m, 0.4 H), 4.97-4.90 (m, 0.4 H), 4.81 (dd, *J* = 3.3, 10.8 Hz, 0.6 H), 3.77 (s, 1.2 H), 3.74 (s, 1.8 H), 3.73 (s, 1.8 H), 3.70 (s, 1.2 H), 3.40 (d, *J* = 8.7 Hz, 0.4 H), 3.32 (d, *J* = 7.8 Hz, 0.6 H), 3.02-2.94 (m, 0.6 H), 2.92-2.60 (comp, 4.4 H), 2.58-2.10 (comp, 2.4 H), 1.56 (q, *J* = 11.4 Hz, 0.6 H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of diastereomers) δ 168.3, 168.2, 168.1, 168.0, 167.6, 136.3, 136.2, 132.9, 132.6, 127.2, 126.5, 122.0, 119.7, 119.6, 118.3, 118.1, 111.2, 110.9, 110.3, 109.0, 60.4, 55.5, 54.3, 53.6, 52.9, 52.7, 52.6, 42.0, 39.9, 36.5, 36.1, 32.8, 31.2, 29.9, 29.8, 21.0, 20.9, 20.8, 14.1; IR (neat) 3256, 2954, 1731, 1621, 1435, 1305, 1234, 1157, 1020, 910, 735 cm^{-1}; mass spectrum (CI) *m/z* 371.1600 [$C_{20}H_{23}N_2O_5$ (M+1) requires 371.1607].

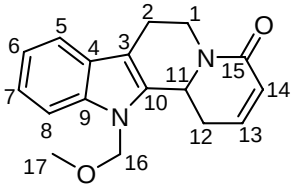


2.16

(3*R, 15*S**)-2-(4-Oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-2-yl)-[1,3]dithiolane-2-carboxylic acid ethyl ester (2.16) (mp2-063).** A solution of *n*-BuLi (0.28 mL, 0.67 mmol) in hexanes (2.44 M) was added to a solution of *i*-Pr_2NH (81 mg, 112 μL, 0.80 mmol) in degassed THF (16 mL) at –78 °C. After stirring at –78 °C for 15 min, the flask was transferred to an ice/water bath and stirring was continued for 15 min. The mixture was then recooled to –78 °C. Neat ethyl-1,3-dithiolane-2-carboxylate (120 mg, 96 μL, 0.67 mmol) was added, and the resulting solution was stirred at –78 °C for 30 min. A solution of **2.17** (80 mg, 0.34 mmol) in degassed THF (16 mL) at -78 °C was added via cannula. The dry ice/acetone bath was removed, and the reaction was stirred for 2 h at room temperature whereupon NH_4Cl (2.0 mL) was added and 50% of the volatiles were removed under reduced pressure. The mixture was poured into a separatory funnel containing 0.5 M HCl (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude mixture of diastereomers (*dr* = 91:9) was separated by flash column-chromatography eluting with hexanes/EtOAc (1:3–100% EtOAc) to afford 84 mg, (60%) of the major diasteromer 2.16 as a pale yellow solid. mp 200-201 °C ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (br s, 1 H), 7.48 (d, *J* = 7.6 Hz, 1 H), 7.39 (d, *J* = 7.6 Hz, 1 H), 7.20 (t, *J* = 7.6 Hz, 1 H), 7.13 (t, *J* = 7.6 Hz, 1 H), 5.03-4.94 (comp, 2 H), 4.32-4.20 (comp, 2 H), 3.49-3.28 (comp, 4 H), 3.12-2.98 (comp, 2 H), 2.79-2.69 (comp, 2 H), 2.68-

2.50 (comp, 3 H), 2.18-2.03 (m, 1 H), 1.29 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 169.3, 136.0, 133.0, 127.4, 122.1, 119.8, 118.1, 111.2, 110.9, 72.9, 62.7, 53.8, 42.6, 40.8, 40.2, 36.6, 35.9, 30.3, 20.9, 14.1; IR (CH_2Cl_2) 3265, 2928, 1714, 1621, 1469, 1445, 1303, 1266, 1212, 1022, 908, 732 cm^{-1}; mass spectrum (CI) m/z 417.1304 [$C_{21}H_{25}N_2O_3S_2$ (M+1) requires 417.1307].

NMR Assignments. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (br s, 1 H, NH), 7.48 (d, J = 7.6 Hz, 1 H, C9-H or C12-H), 7.39 (d, J = 7.6 Hz, 1 H, C9-H or C12-H), 7.20 (t, J = 7.6 Hz, 1 H, C10-H or C11-H), 7.13 (t, J = 7.6 Hz, 1 H, C10-H or C11-H), 5.03-4.94 (comp, 2 H, C3-H, C6-H), 4.32-4.20 (comp, 2 H, C21-H), 3.49-3.28 (comp, 4 H, C18-H, C19-H), 3.12-2.98 (comp, 2 H, C5-H, C6-H), 2.79-2.69 (comp, 2 H, C5-H, C16-H), 2.68-2.50 (comp, 3 H, C14-H, C15-H, C16-H), 2.18-2.03 (m, 1 H, C14-H), 1.29 (t, J = 7.0 Hz, 3 H, C20-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8 (C17), 169.3 (C22), 136.0 (C13), 133.0 (C2), 127.4 (C8), 122.1 (C10 or C11), 119.8 (C10 or C11), 118.1 (C9 or C12), 111.2 (C9 or C12), 110.9 (C7), 72.9 (C23), 62.7 (C21), 53.8 (C3), 42.6 (C6), 40.8 (C18 or C19), 40.2 (C18 or C19), 36.6 (C15), 35.9 (C16), 30.3 (C14), 20.9 (C5), 14.1 (C20).

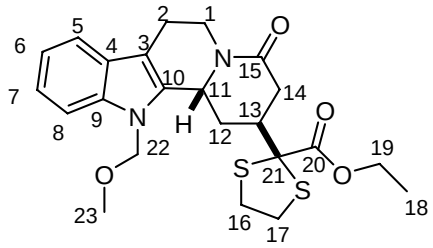


2.24

12-Methoxymethyl-6,7,12,12b-tetrahydro-1*H*-indolo[2,3-*a*]quinolizin-4-one (2.24). (mp1-73). NaH (60% dispersion in mineral oil, 13 mg, 0.321 mmol) was added to a solution of **6** (58.9 mg, 0.247 mmol) in DMF (2.8 mL) at 0 °C. The reaction was stirred for 30 min, and chloromethoxy methane (74 μL, 0.998 mmol) was added. The ice bath

was removed, and the reaction was stirred at room temperature for 2.5 h. Saturated aqueous $NaHCO_3$ (1 mL) and water (10 mL) were added, and the mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (1:3) to give 38 mg (55%) of **2.24** as a white solid: mp 173-175 °C; ^{1}NMR (500 MHz) δ 7.53 (d, *J* = 7.8 Hz, 1 H), 7.42 (d, *J* = 8.4 Hz, 1 H), 7.25 (app td, *J* = 7.2, 2.0 Hz, 1 H), 7.16 (app td, *J* = 7.2, 1.0 Hz, 1 H), 6.67 (ddd, *J* = 9.7, 6.5, 2.1 Hz, 1 H), 6.09 (dd, *J* = 9.7, 2.9 Hz, 1 H), 5.37 (q, *J* = 12.4 Hz, 2 H), 5.04-4.98 (m, 1 H), 4.93 (dd, *J* = 13.6, 4.2 Hz, 1 H), 3.31 (s, 1 H), 3.05 (ddd, *J* = 17.7, 6.5, 4.2 Hz, 1 H), 2.90-2.76 (comp, 3 H), 2.32 (dddd, *J* = 17.7, 13.6, 2.9, 2.1 Hz, 1 H); ^{13}C NMR (500 MHz) δ 164.9, 138.7, 138.4, 133.7, 126.6, 125.6, 122.7, 120.5, 118.6, 112.1, 109.4, 74.4, 56.0, 51.6, 38.4, 31.8, 21.3; IR (neat) 2920, 1661, 1610, 1416, 1307, 1062, 742 cm^{-1}; mass spectrum (CI) *m/z* 283.1434 [$C_{17}H_{18}N_2O_2$ (M+1) requires 283.1447], 251, 283 (base), 297, 323.

NMR Assignments. ^{1}NMR (500 MHz) δ 7.53 (d, *J* = 7.8 Hz, 1 H, C5-H), 7.42 (d, *J* = 8.4 Hz, 1 H, C8-H), 7.25 (app td, *J* = 7.2, 2.0 Hz, 1 H, C7-H), 7.16 (app td, *J* = 7.2, 1.0 Hz, 1 H, C6-H), 6.67 (ddd, *J* = 9.7, 6.5, 2.1 Hz, 1 H, C13-H), 6.09 (dd, *J* = 9.7, 2.9 Hz, 1 H, C14-H), 5.37 (q, *J* = 12.4 Hz, 2 H, C2-H), 5.04-4.98 (m, 1 H, C11-H), 4.93 (dd, *J* = 13.6, 4.2 Hz, 1 H, C11-H), 3.31 (s, 1 H, C17-H), 3.05 (ddd, *J* = 17.7, 6.5, 4.2 Hz, 1 H, C12-H), 2.90-2.76 (comp, 3 H, C2-H & C1-H), 2.32 (dddd, *J* = 17.7, 13.6, 2.9, 2.1 Hz, 1 H, C12-H); ^{13}C NMR (500 MHz) δ 164.9 (C15), 138.7 (C13), 138.4 (C9), 133.7 (C4), 126.6 (C10), 125.6 (C14), 122.7 (C7), 120.5 (C6), 118.6 (C5), 112.1 (C3), 109.4 (C8), 74.4 (C16), 56.0 (C17), 51.6 (C11), 38.4 (C1), 31.8 (C12), 21.3 (C2).

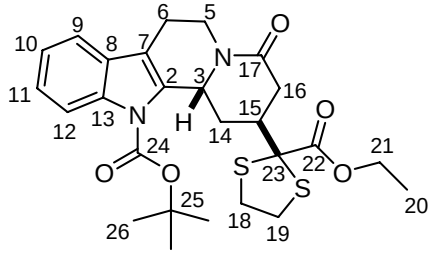


2.25

(3*R, 15*S**)-2-(12-Methoxymethyl-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo-[2,3-*a*]quinolizin-2-yl)-[1,3]dithiolane-2-carboxylic acid ethyl ester (2.25). (mp1-65).** *n*-Butyllithium (2.47 M in hexanes, 67 μL, 0.166 mmol) was added to a solution of diisopropylamine (28μL 0.20 mmol) in THF (0.55 mL) at –78 °C. The reaction was stirred at –78 °C for 15 min and then warmed to 0 °C for 15 min, whereupon it was added via cannula to a solution of **5** (63 mg, 0.15 mmol) in THF (4.5 mL) cooled to –78 °C. The reaction was stirred at -78 °C for 30 min, and chloromethoxy methane (28μL 0.38 mmol) was added and the reaction was allowed to warm to room temperature. After stirring for 40 min, the reaction was diluted with water (5 mL) and 0.5 M HCl (0.5 mL). The aqueous mixture was extracted with EtOAc (3 x 5 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (1:2) to give 15 mg (24%) of recovered starting material **2.16** and 23 mg (32%) of **2.25** as a pale yellow solid: mp 138-141 °C ^{1}H NMR (400 MHz) δ 7.49 (d, *J* = 7.7 Hz, 1 H), 7.41 (d, *J* = 7.9 Hz, 1 H), 7.26-7.19 (m, 1 H), 7.18-7.11 (m, 1 H), 5.43 (s, 2 H), 5.01(dd, *J* = 9.5, 3.7 Hz, 1 H), 4.94-4.83 (m, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.51-3.33 (comp, 4H), 3.27 (s, 3H) 3.08-2.93 (m, 1 H), 2.91-2.74 (comp, 4 H), 2.63 (dd, *J* = 15.4, 11.3 Hz, 1 H), 2.63 (ddd, *J* = 14.4, 4.4, 3.7 Hz, 1 H), 2.14-2.04 (m, 1 H), 1.16 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (500 MHz) δ 171.4, 171.1, 138.1, 133.7, 126.7, 122.5, 120.4, 118.4, 111.8, 109.5, 75.4, 74.3, 62.6, 55.9, 50.9,

40.3, 39.9, 39.8, 36.3, 36.0, 35.0, 20.7, 14,0; IR (neat) 2981, 2921, 1719, 1650, 1460, 1412, 1304, 1213, 1214, 1106, 1063, 1024, 912, cm^{-1}; mass spectrum (CI) *m/z* 461.1556 [$C_{23}H_{29}N_2O_{4S2}$ (M+1) requires 461.1569], 417, 429, 461 (base), 475.

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.49 (d, *J* = 7.7 Hz, 1 H, C5-H), 7.41 (d, *J* = 7.9 Hz, 1 H, C-8H), 7.26-7.19 (m, 1 H, C6-H), 7.18-7.11 (m, 1 H, C6-H), 5.43 (s, 2 H, C22-H), 5.01 (dd, *J* = 9.5, 3.7 Hz, 1 H, C11-H), 4.94-4.83 (m, 1H, C2-H), 4.21 (q, J = 7.1 Hz, 2H, C19-H), 3.51-3.33 (comp, 4H, C16-H & C17-H), 3.27 (s, 3H, C23-H) 3.08-2.93 (m, 1 H, C13-H), 2.91-2.74 (comp, 4 H, C1-H & C2-H & C14-H), 2.63 (dd, *J* = 15.4, 11.3 Hz, 1 H, C14-H), 2.45 (ddd, *J* = 14.4, 4.4, 3.7 Hz, 1 H, C12-H), 2.14-2.04 (m, 1 H, C12-H), 1.16 (t, *J* = 7.1 Hz, 3 H, C18-H). ^{13}C NMR (500 MHz) δ 171.4 (C15), 171.1 (C20), 138.1 (C9), 133.7 (C10), 126.7 (C4), 122.5 (C7), 120.4 (C6), 118.4 (C5), 111.8 (C3), 109.5 (C8), 75.4 (C22), 74.3 (C21), 62.6 (C19), 55.9 (C23), 50.9 (C11), 40.3 (C16 or C17), 39.9 (C16 or C17), 39.8 (C2), 36.3 (C13), 36.0 (C14), 35.0 (C12), 20.7 (C1), 14.0 (C18).

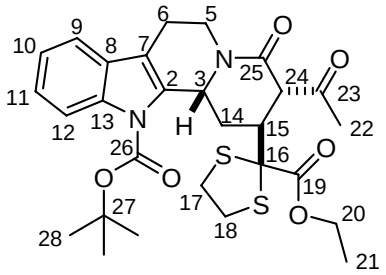


2.31

(3*R, 15*S**)-2-(2-Ethoxycarbonyl-[1,3]dithiolan-2-yl)-4-oxo-1,3,4,6,7,12b-hexahydro-2*H* indolo [2,3-*a*]quinolizine-12-carboxylic acid *tert*-butyl ester (2.31) (mp1-252)** . A solution of **2.16** (550 mg, 1.32 mmol), Boc_2O (1.14 g, 5.28 mmol*)* and dimethylaminopyridine (DMAP) (16 mg, 0.13 mmol) in CH_2Cl_2 (40 mL) was stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure,

and the residue was purified by flash column-chromatography eluting with hexanes/EtOAc (1:2) to give **2.31** (578 mg, 85%) as a white solid. Mp 115-118 °C; ^{1}NMR (500 MHz) δ 7.99 (d, *J* = 8.1 Hz, 1 H), 7.42 (d, *J* = 8.1 Hz, 1 H), 7.28 (m, 1 H), 7.23 (m, 1 H), 5.30-5.26 (m, 1 H), 4.96-4.94 (m, 1H) 4.23-4.10 (m, 1 H), 3.41-3.25 (comp, 4 H), 2.88 (app td, *J* = 11.8, 3.6 Hz, 1 H), 2.84-2.79 (m, 1 H), 2.79-2.73 (m, 1 H), 2.71-2.65 (comp, 2 H), 2.42 (dd, *J* = 14.7, 11.6 Hz, 1 H), 2.99 (ddd, *J* = 14.1, 8.8, 6.0 Hz, 1 H), 2.21-2.15 (m, 1 H), 1.66 (s, 9 H), 1.17 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz) δ 171.2, 171.1, 150.1, 136.7, 134.9, 128.7, 124.6, 123.0, 118.9, 118.3, 115.4, 84.4, 74.6, 62.5, 53.5, 40.5, 40.2, 39.9, 37.1, 35.8, 33.3, 28.2, 21.3, 13.9; IR (neat) 2980, 2924, 1723, 1649, 1453, 1413, 1311, 1214, 1141, 754 cm^{-1}; mass spectrum (CI) *m/z* 517.1830 [$C_{26}H_{32}N_2O_{5S2}$ (M+1) requires 517.1831], 417, 461, 517 (base).

NMR Assignments. ^{1}NMR (500 MHz) δ 7.99 (d, *J* = 8.1 Hz, 1 H, C9-H), 7.42 (d, *J* = 8.1 Hz, 1 H, C12-H), 7.28 (m, 1 H, C10-H), 7.23 (m, 1 H, C11-H), 5.30-5.26 (m, 1 H, C3-H), 4.96-4.91 (m, 1H, C6-H) 4.23-4.10 (m, 1 H, C21-H), 3.41-3.25 (comp, 4 H, C18-H & C19-H), 2.88 (app td, *J* = 11.8, 3.6 Hz, 1 H, C6-H), 2.84-2.79 (m, 1 H, C5-H), 2.79-2.73 (m, 1 H, C16-H), 2.71-2.65 (comp, 2 H, C5-H & C15-H), 2.42 (dd, *J* = 14.7, 11.6 Hz, 1 H, C16-H), 2.99 (ddd, *J* = 14.1, 8.8, 6.0 Hz, 1 H, C14-H), 2.21-2.15 (m, 1 H, C14-H), 1.66 (s, 9 H, C26-H), 1.17 (t, *J* = 7.0 Hz, 3 H, C20-H); ^{13}C NMR (500 MHz) δ 171.2 (C17), 171.1 (C22), 150.1 (C24), 136.7 (C13), 134.9 (C2), 128.7 (C8), 124.6 (C10), 123.0 (C11), 118.9 (C7), 118.3 (C12), 115.4 (C9), 84.4 (C25), 74.6 (C23), 62.5 (C20), 53.5 (C3), 40.5 (C18 or C19), 40.2 (C6), 39.9 (C18 or C19), 37.1 (C15), 35.8 (C16), 33.3 (C14), 28.2 (C21), 21.3 (C5), 13.9 (C21).

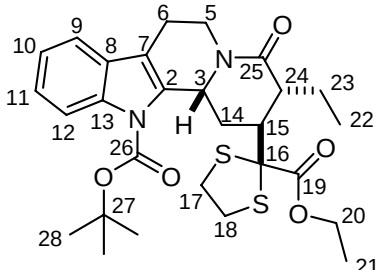


2.30

(3*R, 15*S**, 24*S**)-3-Acetyl-2-(2-ethoxycarbonyl-[1,3dithiolane-2-yl)-4-oxo-1,3,4,6,7,12b-hexahydro-*2H*-indolo[2,3-*α*]quinolizine-12-carboxylic acid *tert*-butyl ester (2.30) (mp1-226).** A solution of potassium hexamethyldisilazide in toluene (0.58 mL of 0.5 M, 0.291 mmol) was added dropwise over 10 min to a solution of **2.31** (50 mg, 0.097 mmol) and $MgBr_2 \cdot OEt_2$ (27 mg, 0.101 mmol) in THF (1 mL, degassed by three freeze-pump-thaw cycles) at -78 °C. The reaction was stirred at -78 °C for 2 h whereupon a solution of freshly distilled acetyl chloride (23 mg, 21 μL, 0.291 mmol) in degassed THF (1 mL) cooled to -78 °C was added via cannula. The solution was stirred at -78 °C for 2 h, whereupon a saturated aqueous solution of NH_4Cl (0.2 mL) was added. The cooling bath was removed and the mixture was stirred at room temperature for 40 min. The slurry was diluted with EtOAc (5 mL) and poured into a separatory funnel containing 0.5 M HCl (3 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by flash chromatography eluting with hexanes/EtOAc (1:2) to give 32 mg (60%, *dr* > 95:5) of **2.30** as a pale yellow solid: mp 141-144 °C; ^{1}NMR (500 MHz) δ 7.90 (d, *J* = 8.2 Hz, 1 H), 7.43-7.39 (m, 1 H), 7.28-7.25 (m, 1 H), 7.24-7.20 (m, 1 H), 5.45-5.41 (m, 1 H), 5.10-5.05 (m, 1H) 4.29-4.23 (comp, 2 H), 4.03 (d, *J* = 4.0 Hz, 1 H), 3.54-3.43 (comp, 2 H), 3.39-3.27 (comp, 3 H), 2.85-2.78 (m, 1 H), 2.73-2.67 (m, 1 H), 2.67-2.57 (m, 1 H), 2.43

(s, 3 H), 1.93 (ddd, *J* = 14.7, 11.0, 6.4 Hz, 1 H), 1.67 (s, 9 H), 1.29 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (500 MHz) δ 205.1, 170.9, 166.9, 150.3, 136.3, 134.9, 128.7, 124.5, 122.9, 118.5, 118.3, 115.5, 84.3, 74.3, 62.4, 56.6, 52.7, 41.4, 39.4, 39.1, 38.2, 31.3, 30.8, 28.2, 21.6, 13.9; IR (neat) 2975, 2923, 1723, 1635, 1453, 1422, 1365, 1308, 1219, 1136, 1022, 747 cm^{-1}; mass spectrum (CI) *m/z* 559.1939 [$C_{28}H_{35}N_2O_6S_2$ (M+1) requires 559.1937], 279, 381, 459, 517, 559 (base).

NMR Assignments. ^{1}NMR (500 MHz) δ 7.90 (d, *J* = 8.2 Hz, 1 H, C9-H), 7.43-7.39 (m, 1 H, C12-H), 7.28-7.25 (m, 1 H, C10-H), 7.24-7.20 (m, 1 H, C11-H), 5.45-5.41 (m, 1 H, C3-H), 5.10-5.05 (m, 1 H, C6-H) 4.29-4.23 (comp, 2 H, C20-H), 4.03 (d, *J* = 4.0 Hz, 1H, C24-H), 3.54-3.43 (comp, 2 H, C17-H, C18-H), 3.39-3.27 (comp, 3 H, C17-H, C18-H, C15-H), 2.85-2.78 (m, 1 H, C6-H), 2.73-2.67 (m, 1 H, C14-H), 2.67-2.57 (m, 1 H, C14-H), 2.43 (s, 3 H, C22-H), 1.93 (ddd, *J* = 14.7, 11.0, 6.4 Hz, 1 H, C14-H), 1.67 (s, 9 H) , C28-H, 1.29 (t, *J* = 7.23 Hz, 3 H, C21-H); ^{13}C NMR (500 MHz) δ 205.1 (C23), 170.9 (C25), 166.9 (C19), 150.3 (C26), 136.3 (C13), 134.9 (C2), 128.7 (C8), 124.5 (C10), 122.9 (C11), 118.5 (C7), 118.3 (C12), 115.5 (C9), 84.3 (C27), 74.3 (C16), 62.4 (C20), 56.6 (C24), 52.7 (C3), 41.4 (C17 or C18), 39.4 (C6), 39.1 (C17 or C18), 38.2 (C15), 31.3 (C14), 30.8 (C22), 28.2 (C28), 21.6 (C5), 13.9 (C21).



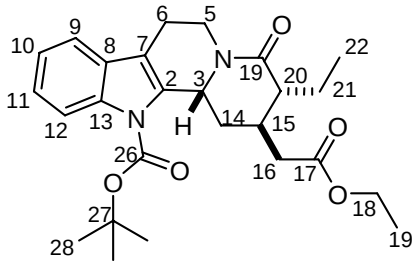
2.33

(3*R, 15*R**, 24*S**)-2-(2-Ethoxycarbonyl-[1,3]dithiolane-2-yl)-3-ethyl-4-oxo-1,3,4,6,7,12b-hexa hydro-*2H*-indolo[2,3-*α*]quinolizine-12-carboxylic acid *tert*-butyl**

ester (2.33) (mp2-120). A solution of sodium hexamethyldisilazide in THF (0.39 mL, 2.0 M, 0.774 mmol) was added dropwise over 12 min to a solution of 2.31 (200 mg, 0.387 mmol) in degassed THF (2.5 mL) at –78 °C. The mixture was stirred at –78 °C for 1 h, whereupon it was cooled –100 °C. 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)- pyrimidone (DMPU) (74 mg, 70 μL, 0.58 mmol) was added followed by ethyl triflate (276 mg, 0.20 mL, 1.55 mmol). The mixture was stirred at –100 °C for 2.5 h, whereupon benzylamine (249 mg, 0.25 mL, 2.32 mmol) and ethanol (0.2 mL) were added. The flask was transferred to a –78 °C bath and stirring was continued for 45 min. A saturated aqueous solution of NH_4Cl (2 mL) was added and the cold bath was removed. After allowing the reaction to warm to room temperature, the mixture was poured into a separatory funnel containing 0.5 M HCl (10 mL) and EtOAc (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column-chromatography eluting with pentane/acetone (2:1) to give 39 mg (20%) of recovered 2.31 and 142 mg (67%, *dr* > 95:5) of 2.33 as a colorless foam that could be recrystallized from CH_2Cl_2/heptane. mp 151-153 °C; ^{1}NMR (500 MHz) δ 7.91-7.87 (m, 1 H), 7.43-7.40 (m, 1 H), 7.27-7.20 (comp, 2 H), 5.41-5.35 (m, 1 H), 5.18-5.12 (m, 1H), 4.32 (q, *J* = 7.2 Hz, 2 H), 3.50-3.44 (comp, 2 H), 3.34-3.25 (comp, 3 H), 2.86-2.65 (comp, 6 H), 1.97-1.88 (m, 1 H), 1.76 (ddd, *J* = 14.3, 11.8, 4.8 Hz, 1 H), 1.67 (s, 9 H), 1.60-1.50 (m, 1H), 1.34 (t, *J* = 7.2 Hz, 3 H), 1.00 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (125 MHz) δ 172.7, 171.3, 150.3, 136.5, 135.9, 128.9, 124.4, 122.9, 118.5, 118.3, 115.5, 84.2, 74.1, 62.2, 53.0, 44.6, 41.7, 39.5, 39.2, 38.7, 28.5, 28.2, 27.2, 22.0, 13.9, 12.1; IR (neat) 2975, 2923, 1723, 1635, 1453, 1417, 1370, 1303, 1219, 1136, 1022, 731 cm^{-1}; mass

spectrum (CI) *m/z* 545.2143 [$C_{28}H_{37}N_2O_5S_2$ (M+1) requires 545.2144], 233, 339, 445, 545 (base).

NMR Assignments. ^{1}NMR (500 MHz) δ 7.91-7.87 (m, 1 H, C9-H), 7.43-7.40 (m, 1 H, C12-H), 7.27-7.20 (comp, 2 H, C10-H, C11-H), 5.41-5.35 (m, 1 H, C3-H), 5.18-5.12 (m, 1H, C6-H), 4.32 (q, *J* = 7.2 Hz, 2 H, C20-H), 3.50-3.44 (comp, 2 H, C17-H, C18-H), 3.34-3.25 (comp, 3 H, C15-H, C17-H, C18-H), 2.86-2.65 (comp, 6 H, C5-H, C6-H, C14-H, C24-H), 1.97-1.88 (m, 1 H, C23-H), 1.76 (ddd, *J* = 14.3, 11.8, 4.8 Hz, 1 H, C23-H), 1.67 (s, 9 H, C14-H), 1.60-1.50 (m, 1H, C23-H), 1.34 (t, *J* = 7.2 Hz, 3 H, C21-H), 1.00 (t, *J* = 7.4 Hz, 3 H, C22-H); ^{13}C NMR (125 MHz) δ 172.7 (C25), 171.3 (C19), 150.3 (C26), 136.5 (C13), 135.9 (C2), 128.9 (C8), 124.4 (C10), 122.9 (C11), 118.5 (C7), 118.3 (C12), 115.5 (C9), 84.2 (C27), 74.1 (C16), 62.2 (C20), 53.0 (C3), 44.6 (C24), 41.7 (C17 or C18), 39.5 (C15), 39.2 (C6), 38.7 (C17 or C18), 28.5 (C14), 28.2 (C28), 27.2 (C23), 22.0 (C5), 13.9 (C21), 12.1 (C22); IR (neat) 2975, 2923, 1723, 1635, 1453, 1417, 1370, 1303, 1219, 1136, 1022, 731 cm^{-1}; mass spectrum (CI) *m/z* 545.2143 [$C_{28}H_{37}N_2O_5S_2$ (M+1) requires 545.2144], 233, 339, 445, 545 (base).



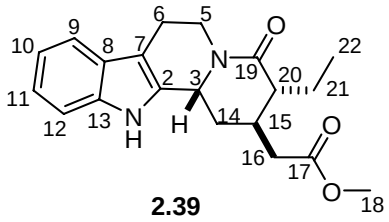
2.36

(3*R, 15*S**, 22*S**)-2-(2-Ethoxycarbonyl-3-ethyl-4-oxo-1,3,4,6,7,12b-hexa hydro-*2H*-indolo [2,3-*α*]quinolizine-12-carboxylic acid *tert*-butyl ester (45) (mp2-125).** A slurry of Raney-Nickel in water (2.9 g) was added to a solution of **2.33** (312 mg,

0.57 mmol) in EtOH (20 mL), and the reaction was stirred at room temperature for 4 h. EtOAc (20 mL) was added and the mixture was dried (Na_2SO_4) and filtered through Celite. The solids were washed with EtOAc (20 mL) and the filtrate was concentrated under reduced pressure. Purification of the residue by flash column-chromatography eluting with hexane/EtOAc (1:1) gave 242 mg (93%) of **2.36** as a clear colorless oil; ^{1}NMR (125 MHz) δ 7.94-7.90 (m, 1 H), 7.44-7.39 (m, 1 H), 7.30-7.20 (comp, 2 H), 5.21-5.18 (m, 1 H), 5.06-5.03 (m, 1 H), 4.15 (q, *J* = 7.0 Hz, 2 H), 2.83-2.76 (m, 1 H), 2.72-2.67 (comp, 2 H), 2.61 (dd, *J* = 15.9, 7.4 Hz, 1 H), 2.52 (dd, *J* = 15.9, 7.4 Hz, 1 H), 2.48-2.37 (comp, 3 H), 2.21-2.15 (m, 1 H), 1.87-1.79 (m, 1 H), 1.75-1.64 (comp, 10 H), 1.56-1.52 (m, 1 H), 1.27 (t, *J* = 7.0 Hz, 3 H), 0.98 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (500 MHz) δ 172.2, 172.0, 150.3, 136.5, 135.7, 128.8, 124.4, 122.9, 118.4, 118.3, 115.5, 84.3, 60.5, 51.8, 47.6, 39.2, 38,1, 30.5, 29.7, 28.2, 25.5, 21.7, 14.2, 12.1; IR (neat) 2970, 2927, 1728, 1656, 1640, 1455, 1414, 1368, 1311, 1249, 1219, 1158, 1136, 1116, 745 cm^{-1}; mass spectrum (CI) *m/z* 455.2559 [$C_{26}H_{35}N_2O_5$ (M+1) requires 455.2546], 355, 399, 455 (base).

NMR Assignments. ^{1}NMR (500 MHz) δ 7.94-7.90 (m, 1 H, C9-H), 7.44-7.39 (m, 1 H, C12-H), 7.30-7.20 (comp, 2 H, C10-H, C11-H), 5.21-5.18 (m, 1 H, C3-H), 5.06-5.03 (m, 1 H, C6-H), 4.15 (q, *J* = 7.0 Hz, 2 H, C18-H), 2.83-2.76 (m, 1 H, C6-H), 2.72-2.67 (comp, 2 H, C5-H), 2.61 (dd, *J* = 15.9, 7.4 Hz, 1 H, C16-H), 2.52 (dd, *J* = 15.9, 7.4 Hz, 1 H, C16-H), 2.48-2.37 (comp, 3 H, C14-H, C15-H), 2.21-2.15 (m, 1 H, C20-H), 1.87-1.79 (m, 1 H, C21-H), 1.75-1.64 (comp, 10 H, C14-H, C26-H), 1.56-1.52 (m, 1 H, C21-H), 1.27 (t, *J* = 7.0 Hz, 3 H, C19-H), 0.98 (t, *J* = 7.4 Hz, 3 H, C22-H); ^{13}C NMR (500 MHz) δ 172.2 (C23), 172.0 (C17), 150.3 (C24), 136.5 (C13), 135.7 (C2), 128.8 (C8), 124.4 (C10), 122.9 (C11), 118.4 (C7), 118.3 (C12), 115.5 (C9), 84.3 (C25), 60.5

(C18), 51.8 (C3), 47.6 (C20), 39.2 (C6), 38.1 (C16), 30.5 (C14), 29.7 (C15), 28.2 (C26), 25.5 (C21), 21.7 (C5), 14.2 (C19), 12.1 (C22).

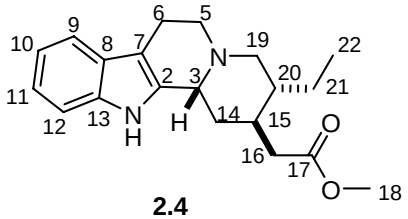


2.39

(3*R, 15*S**, 20R*)-3-Ethyl-4-oxo-1,2,3,4,6,7,12b-octahydroindolo[2,3-*α*]quinolizine-2-yl]-acetic acid methyl ester (2.39) (mp2-127).** A solution of 4.4 M NaOMe (1.20 mL, 5.28 mmol), which was freshly prepared by the addition of sodium (404 mg, 17.6 mmol) to degassed methanol (4 mL), was added to a solution of **2.36** (240 mg, 0.53 mmol) in degassed THF (5 mL) at 0 °C. The ice bath was removed, and the reaction was stirred at room temperature for 1 h, whereupon the reaction was cooled to 0 °C, and a saturated aqueous solution of NH_4Cl (3 mL) and water (15 mL) were added. The mixture was poured into a separatory funnel containing EtOAc (20 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 15 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was recrystallized from CH_2Cl_2/ether and the mother liquor was purified by flash chromatography eluting with hexane/EtOAc (1:1) to afford a total of 155 mg (86%) of **2.39** as a white solid: mp 186-189 °C decomp.; ^{1}NMR (500 MHz, $CDCl_3$) δ 7.92 (br s, 1H), 7.48 (d, *J* = 7.6 Hz, 1 H), 7.33 (d, *J* = 8.0 Hz, 1 H), 7.19-7.15 (m, 1 H), 7.12-7.09 (m, 1 H), 5.14-5.08 (m, 1 H), 4.83 (dd, *J* = 9.4, 5.2 Hz, 1 H), 3.72 (s, 3 H), 2.89-2.81 (comp, 2 H), 2.77-2.70 (m, 1 H), 2.55-2.38 (comp, 3 H), 2.25-2.19 (comp, 2 H), 2.17-2.11 (m, 1 H), 1.82-1.74 (m, 1 H), 1.64-1.55 (m, 1 H), 0.92 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (125 MHz) δ 172.5, 171.0, 136.2, 133.1, 127.0, 122.2, 119.9, 118.3,

111.0, 110.0, 51.8, 50.7, 48.2, 40.7, 37.3, 29.4, 28.6, 24.9, 21.1, 11.8; IR (neat) 3255, 2962, 2930, 1733, 1612, 1466, 1434, 1351, 1304, 1262, 1236, 1199, 1168, 739 cm^{-1}; 340.1777 [$C_{20}H_{24}N_2O_3S_2$ (M+) requires 340.1787], 241, 273, 305, 341 (base), 369.

NMR Assignments. ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 (br s, 1H, NH), 7.48 (d, *J* = 7.6 Hz, 1 H, C9-H or C12-H), 7.33 (d, *J* = 8.0 Hz, 1 H, C9-H or C12-H), 7.19-7.15 (m, 1 H, C10-H or C11-H), 7.12-7.09 (m, 1 H, C10-H or C11-H), 5.14-5.08 (m, 1 H, C6-H), 4.83 (dd, *J* = 9.4, 5.2 Hz, 1 H, C3-H), 3.72 (s, 3 H, C18-H), 2.89-2.81 (comp, 2 H, C5-H and C6-H), 2.77-2.70 (m, 1 H, C5-H), 2.55-2.38 (comp, 3 H, C15-H and C16-H), 2.25-2.19 (comp, 2 H, C14-H and C20-H), 2.17-2.11 (m, 1 H, C14-H), 1.82-1.74 (m, 1 H, C21-H), 1.64-1.55 (m, 1 H, C21-H), 0.92 (t, *J* = 7.4 Hz, 3 H, C22-H); ^{13}C NMR (125 MHz) δ 172.5 (C17), 171.0 (C19), 136.2 (C13), 133.1 (C2), 127.0 (C8), 122.2 (C10 or C11), 119.9 (C10 or C11), 118.3 (C9 or C12), 111.0 (C9 or C12), 110.0 (C7), 51.8 (C18), 50.7 (C3), 48.2 (C20), 40.7 (C6), 37.3 (C16), 29.4 (C15), 28.6 (C14), 24.9 (C21), 21.1 (C5), 11.8 (C22).



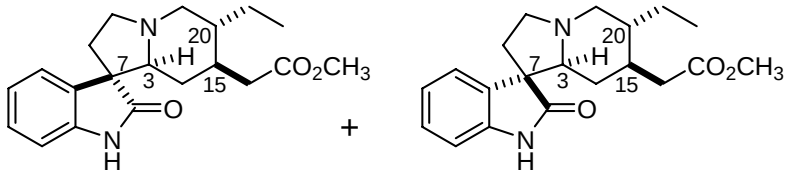
2.4

(3*R, 15*S**, 20*S**)-3-Ethyl-4-oxo-1,2,3,4,6,7,12b-octahydro-indolo[2,3-*a*]quinolizine-2-yl]-acetic acid methyl ester (2.4) (mp2-131).** A slurry of **2.39** (72 mg, 0.21 mmol), trimethyloxonium tetrafluoroborate (83 mg, 0.56 mmol) and 2,6-di-*tert*-butylpyridine (118 mg, 0.14 mL, 0.619 mmol) in CH_2Cl_2 (7 mL) was stirred at room temperature for 21 h during which time a homogenous yellow solution was produced. The reaction mixture was cooled to 0 °C, and anhydrous MeOH (2.5 mL) was added.

After 15 min, $NaBH_4$ (83 mg, 2.18 mmol) was added, and the reaction mixture was stirred for an additional 20 min. Saturated $NaHCO_3$ (5 mL) and CH_2Cl_2 (10 mL) were added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 8 mL). The combined organic fractions were dried (Na_2SO_4), and the volatiles were removed under reduced pressure. The residue was purified by flash chromatography eluting with 2.5%–10% MeOH in CH_2Cl_2 to afford 56 mg (81%) of **2.4** as a foam. ^{1}NMR (500 MHz, $CDCl_3$) δ 8.00 (br s, 1H), 7.50 (d, *J* = 7.4 Hz, 1 H), 7.40-7.38 (m, 1 H), 7.18 (app td, *J* = 7.4, 1.2 Hz, 1 H), 7.12 (app td, *J* = 7.4, 1.2 Hz, 1 H), 4.13 (br s, 1 H), 3.75 (s, 3 H), 3.23 (dd, *J* = 11.9, 5.2 Hz, 1 H), 3.10 (dd, *J* = 11.9, 4.4 Hz, 1 H), 3.08-2.99 (m, 1 H), 2.76 (dd, *J* = 11.4, 3.4 Hz, 1 H), 2.69-2.64 (m, 1 H), 2.63 (dd, *J* = 16.3, 4.4 Hz, 1 H), 2.56 (dd, *J* = 11.4, 8.0 Hz, 1 H), 2.31-2.24 (comp, 2 H), 1.82-1.74 (comp, 2 H), 1.58-1.49 (m, 1 H), 1.46-1.38 (m, 1 H), 1.27-1.19 (m, 1 H), 0.87 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (125 MHz) δ 173.7, 136.0, 133.2, 127.6, 121.4, 119.4, 118.0, 111.1, 107.8, 54.3, 51.9, 51.6, 51.4, 41.2, 36.9, 32,8, 32.2, 24.1, 18.5, 11.5; IR (neat) 3397, 3245, 2941, 1731, 1452, 1168, 1004, 732 cm^{-1}; mass spectrum (CI) *m/z* 327.2076 [$C_{20}H_{27}N_2O_2$ (M+1) requires 327.2073], 325, 327 (base), 326, 341.

NMR Assignments. ^{1}NMR (500 MHz) δ 8.00 (br s, 1H, NH), 7.50 (d, *J* = 7.4 Hz, 1 H, C9-H or C12-H), 7.40-7.38 (m, 1 H, C9-H or C12-H), 7.18 (app dt, *J* = 7.4, 1.2 Hz, 1 H, C10-H or C11-H), 7.12 (app dt, *J* = 7.4, 1.2 Hz, 1 H, C10-H or C11-H), 4.13 (br s, 1 H, C3-H), 3.75 (s, 3 H, C18-H), 3.23 (dd, *J* = 11.9, 5.2 Hz, 1 H, C6-H), 3.10 (dd, *J* = 11.9, 4.4 Hz, 1 H, C6-H), 3.08-2.99 (m, 1 H, C5-H), 2.76 (dd, *J* = 11.4, 3.4 Hz, 1 H, C19-H), 2.69-2.64 (m, 1 H, C5-H), 2.63 (dd, *J* = 16.3, 4.4 Hz, 1 H, C16-H), 2.56 (dd, *J* = 11.4, 8.0 Hz, 1 H, C19-H), 2.31-2.24 (comp, 2 H, C14-H and C16-H), 1.82-1.74 (comp, 2 H, C14-H and C-15), 1.58-1.49 (m, 1 H, C21-H), 1.46-1.38 (m, 1 H, C20-H), 1.27-1.19 (m,

1 H, C21-H), 0.87 (t, J = 7.4 Hz, 3 H, C22-H); ^{13}C NMR (125 MHz) δ 173.7 (C17), 136.0 (C13), 133.2 (C2), 127.6 (C8), 121.4 (C10 or C11), 119.4 (C10 or C11), 118.0 (C9 or C12), 111.1 (C9 or C12), 107.8 (C7), 54.3 (C3), 51.9 (C6), 51.6 (C18), 51.4 (C19), 41.2 (C20), 36.9 (C16), 32,8 (C15), 32.2 (C14), 24.1 (C21), 18.5 (C5), 11.5 (C22).



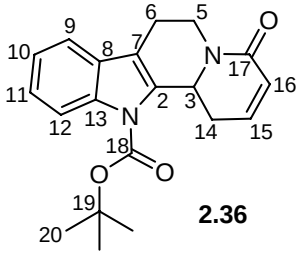
epi-**2.3** **2.3**

Spirooxindoles epi-2.3 and 2.3 (mp2-146, mp2-147, mp2-149). A solution of *t*-BuOCl in CCl_4 (0.5 M, 0.50 mL, 0.25 mmol) was added to a solution of **2.4** (51 mg, 0.16 mmol) in CH_2Cl_2 (11 mL) at –20 °C. The reaction mixture was stirred at –20 °C for 0.5 h, and the volatiles were removed under reduced pressure. The yellow residue was dissolved in MeOH (7 mL) and a freshly prepared solution of $NaOCH_3$ (3.5 M, 0.9 mL, 3.15 mmol) was added. The reaction mixture was stirred for 4 h at room temperature, whereupon saturated aqueous $NaHCO_3$ (6 mL) and brine (6 mL) were added. The aqueous mixture was extracted with Et_2O (3 x 10 mL), and the combined organic layers were dried (Na_2SO_4). The volatiles were evaporated under reduced pressure, and the residue was dissolved in CH_2Cl_2 (13 mL). Water (2.2 mL) was added, the mixture was cooled to 0 °C, and CF_3SO_3H (0.14 mL, 1.56 mmol) was added via syringe. The reaction was stirred at 0 °C for 1 h and then for an additional 5 h at room temperature. A saturated aqueous solution of $NaHCO_3$ (4 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. From the ^{1}H NMR of the crude product a *dr* = 45:55 of *epi*-**3**/**3** was determined. The crude mixture was

separated by flash chromatography eluting with EtOAc/hexanes (2:1 → 100% EtOAc) then 1% → 2 % MeOH in EtOAc to give 18 mg (35%) of *epi*-**2.3** (less polar) as a yellow oil and 22 mg (41%) **2.3** (more polar) as a colorless solid; mp = 172-174 °C (Et_2O/pentane); Lit.[27] 167-168 °C. *epi*-**2.3**: ^{1}NMR (500 MHz, DMSO d_6) δ 10.32 (s, 1 H), 7.21 (d, *J* = 7.4 Hz, 1 H), 7.14 (td, *J* = 7.6, 1.2 Hz, 1 H), 6.94 (td, *J* = 7.4, 0.8 Hz, 1 H), 6.80 (d, *J* = 7.6, Hz, 1 H), 3.46 (s, 3 H), 3.24-3.17 (comp, 2 H), 2.45 (dd, *J* = 15.5, 3.8 Hz, 1 H), 2.30 (app q, *J* = 8.7 Hz, 1 H) 2.22 (dd, *J* = 11.3, 2.3 Hz, 1 H), 2.16 (ddd, *J* = 12.8, 9.5, 2.4 Hz, 1 H), 1.90-1.79 (comp, 2 H), 1.69 (app t, *J* = 10.9 Hz, 1 H), 1.52-1.44 (m, 1 H), 1.42-1.34 (m, 1 H), 1.20-1.12 (m, 1 H), 1.08-0.98 (comp, 2 H), 0.82 (t, *J* = 7.4 Hz, 3 H), 0.60 (app q, *J* = 11.9, 1 H); ^{13}C NMR (125 MHz, DMSO d_6) δ 179.9, 172.6, 141.4, 133.5, 127.4, 124.3, 121.4, 109.1, 70.9, 56.9, 55.9, 53.2, 51.1, 40.5, 37.3, 36.6, 34.6, 31.5, 22.7, 10.7; IR (neat) , 3208, 2932, 2804, 1726, 1708, 1619, 1470, 1342, 1223, 1167, 754 cm^{-1}; mass spectrum (CI) *m/z* 343.2032 [$C_{20}H_{26}N_2O_3$ (M+1) requires 343.2022], 197, 311, 343 (base). **2.3** : ^{1}NMR (500 MHz, DMSO d_6) δ 10.15 (s, 1 H, NH), 7.23 (d, *J* = 9.2 Hz, 1 H), 7.14 (t, *J* = 7.3, Hz, 1 H), 6.95 (t, *J* = 7.4, Hz, 1 H), 6.77 (d, *J* = 7.6, Hz, 1 H), 3.48 (s, 3 H), 3.16-3.12 (comp, 2 H), 2.51-2.47 (multiplicity obscured by DMSO peak, 1 H), 2.40-2.34 (m, 1 H) 2.18-2.10 (comp, 2 H), 2.00 (dd, *J* = 15.5, 8.6 Hz, 1 H), 1.85 (dd, *J* = 12.4, 7.4 Hz, 1 H), 1.64 (app t, *J* = 10.7 Hz, 1 H), 1.54-1.45 (m, 1 H), 1.36-1.08 (comp, 4 H), 1.04-0.96 (m, 1 H), 0.81 (t, *J* = 7.4 Hz); ^{13}C NMR (125 MHz, DMSO d_6) δ 179.6, 172.7, 141.8, 133.8, 127.7, 123.1, 121.6, 108.8, 73.8, 56.4, 55.1, 54.0, 51.1, 37.4, 36.9, 34.3, 30.8, 22.8, 10.7; IR (neat) , 3233, 2935, 2779, 1727, 1619, 1476, 1333, 1219, 1178, 758 cm^{-1}; mass spectrum (CI) *m/z* 343.2018 [$C_{20}H_{26}N_2O_3$ (M+1) requires 343.2022], 343 (base), 371.

NMR Assignments. *epi*-**2.3**: ^{1}NMR (500 MHz, DMSO d_6) δ 10.32 (s, 1 H, NH), 7.21 (d, *J* = 7.4 Hz, 1 H, C9-H), 7.14 (td, *J* = 7.6, 1.2 Hz, 1 H, C11-H), 6.94 (td, *J* = 7.4,

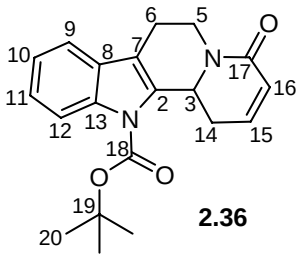
0.8 Hz, 1 H, 10-H), 6.80 (d, *J* = 7.6, Hz, 1 H, C12-H), 3.46 (s, 3 H, C22-H), 3.24-3.17 (comp, 2 H, C5-H, C21-H), 2.45 (dd, *J* = 15.5, 3.8 Hz, 1 H, C16-H), 2.30 (app q, *J* = 8.7 Hz, 1 H, C5-H) 2.22 (dd, *J* = 11.3, 2.3 Hz, 1 H, C3-H), 2.16 (ddd, *J* = 12.8, 9.5, 2.4 Hz, 1 H, C6-H), 1.90-1.79 (comp, 2 H, C6-H, C16-H), 1.69 (app t, *J* = 10.9 Hz, 1 H, C21-H), 1.52-1.44 (m, 1 H, C19-H), 1.42-1.34 (m, 1 H, C15-H), 1.20-1.12 (m, 1 H, C20-H), 1.08-0.98 (comp, 2 H, C14-H, C19-H), 0.82 (t, *J* = 7.4 Hz, 3 H, C18-H), 0.60 (app q, *J* = 11.9, 1 H, C14-H); ^{13}C NMR (125 MHz, DMSO d_6) δ 179.9 (C2), 172.6 (C17), 141.4 (C13), 133.5 (C8), 127.4 (C11), 124.3 (C9), 121.4 (C10), 109.1 (C12), 70.9 (C3), 56.9 (C21), 55.9 (C7), 53.2 (C5), 51.1 (C22), 40.5 (C20), 37.3 (C16), 36.6 (C15), 34.6 (C6), 31.5 (C14), 22.7 (C19), 10.7 (C18). **2.3**: ^{1}NMR (500 MHz, DMSO d_6) δ 10.15 (s, 1 H, NH), 7.23 (d, *J* = 9.2 Hz, 1 H, C9-H), 7.14 (t, *J* = 7.3, Hz, 1 H, C11-H), 6.95 (t, *J* = 7.4, Hz, 1 H, C10-H), 6.77 (d, *J* = 7.6, Hz, 1 H, C12-H), 3.48 (s, 3 H, C22-H), 3.16-3.12 (comp, 2 H, C5-H, C21-H), 2.51-2.47 (multiplicity obscured by DMSO peak, 1 H, C16-H), 2.40-2.34 (m, 1 H, C5-H) 2.18-2.10 (comp, 2 H, C3-H, C6-H), 2.00 (dd, *J* = 15.5, 8.6 Hz, 1 H, C16-H), 1.85 (dd, *J* = 12.4, 7.4 Hz, 1 H, C6-H), 1.64 (app t, *J* = 10.7 Hz, 1 H, C21-H), 1.54-1.45 (m, 1 H, C19-H), 1.36-1.08 (comp, 4 H, C14-H, C15-H, C20-H), 1.04-0.96 (m, 1 H, C19-H), 0.81 (t, *J* = 7.4 Hz, C18-H); ^{13}C NMR (125 MHz, DMSO d_6) δ 179.6 (C2), 172.7 (C17), 141.8 (C13), 133.8 (C28), 127.7 (C11), 123.1 (C9), 121.6 (C10), 108.8 (C12), 73.8 (C3), 56.4 (C21), 55.1 (C7), 54.0 (C5), 51.1 (C22), 37.4 (C16), 36.9 (C15), 34.3 (C6), 30.8 (C14), 22.8 (C19), 10.7 (C18).



2.36

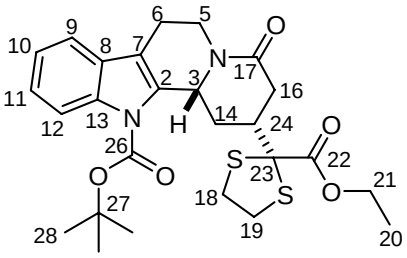
4-Oxo-1,6,7,12b-tetrahydro-4*H*-indolo[2,3-*a*]quinolizine-12-carboxylic acid *tert*-butyl ester (2.36) (mp1-300). A solution of **2.17** (1.10 g, 4.62 mmol), Boc_2O (4.97 g, 23.1 mmol*)* and dimethylaminopyridine (DMAP) (113 mg, 0.92 mmol) in THF (100 mL) was stirred at room temperature for 4 h, whereupon the reaction was concentrated under reduced pressure. The residue was purified by flash column-chromatography eluting with hexanes/EtOAc (1:1–1:2) to give 1.54 g (99%) of **2.36** as a white solid: mp 181-183 °C; ^{1}NMR (500 MHz) δ 8.06 (d, *J* = 8.2 Hz, 1 H), 7.47-7.45 (m, 1 H), 7.32-7.28 (m, 1 H), 7.27-7.24 (m, 1 H), 6.67 (ddd, *J* = 9.6, 6.5, 2.1 Hz, 1 H), 6.07 (dd, *J* = 9.6, 2.9 Hz, 1 H) 5.26-5.21 (m, 1 H), 5.00 (ddd, *J* = 12.7, 4.6, 1.6 Hz, 1 H), 3.01 (ddd, *J* = 17.1, 6.5, 3.6 Hz, 1 H), 2.87-2.79 (comp, 3 H), 2.15 (dddd, *J* = 17.1, 13.1, 2.9, 2.1, Hz, 1 H), 1.67 (s, 9 H); ^{13}C NMR (125 MHz) δ 164.8, 150.0, 139.1, 136.6, 134.1, 128.5, 125.4, 124.7, 123.1, 118.4, 118.0, 115.8, 84.5, 53.3, 37.6, 31.6, 28.2, 21.5; IR ($CDCl_3$) 2982, 2919, 1727, 1659, 1607, 1423, 1366, 1308, 1146, 1052, 817, 718 cm^{-1}; mass spectrum (CI) *m/z* 339.1721 [$C_{20}H_{23}N_2O_3$ (M+1) requires 339.1709], 283, 311, 339 (base), 367, 422.

NMR Assignments. ; ^{1}NMR (500 MHz) δ 8.06 (d, *J* = 8.2 Hz, 1 H, C9-H), 7.47-7.45 (m, 1 H, C12-H), 7.32-7.28 (m, 1 H, C10-H), 7.27-7.24 (m, 1 H, C11-H), 6.67 (ddd, *J* = 9.6, 6.5, 2.1 Hz, 1 H, C15-H), 6.07 (dd, *J* = 9.6, 2.9 Hz, 1 H, C16-H) 5.26-5.21 (m, 1 H, C3-H), 5.00 (ddd, *J* = 12.7, 4.6, 1.6 Hz, 1 H, C6-H), 3.01 (ddd, *J* = 17.1, 6.5, 3.6 Hz, 1 H, C14-H), 2.87-2.79 (comp, 3 H, C6-H, C5-H), 2.15 (dddd, *J* = 17.1, 13.1, 2.9, 2.1 Hz, 1 H, C14-H), 1.67 (s, 9 H, C20-H); ^{13}C NMR (500 MHz) δ 164.8 (C17), 150.0 (C18), 139.1 (C15), 136.6 (C13), 134.1 (C2), 128.5 (C8), 125.4 (C16), 124.7 (C10), 123.1 (C11), 118.4 (C7), 118.0 (C12), 115.8 (C9), 84.5 (C19), 53.3 (C3), 37.6 (C6), 31.6 (C14), 28.2 (C20), 21.5 (C5).



2.36

4-Oxo-1,6,7,12b-tetrahydro-4*H*-indolo[2,3-*a*]quinolizine-12-carboxylic acid *tert*-butyl ester (2.36) (mp2-046). To a degassed solution of Grubbs' first-generation catalyst (18 mg, 0.02 mmol, 4 mol%) in CH_2Cl_2 (25 mL) was added a solution of **2.17** (149 mg, 0.56 mmol) in degassed CH_2Cl_2 (7 mL) via cannula. The reaction mixture was stirred at room temperature for 24 h, whereupon Boc_2O (603 mg, 2.80 mmol) and dimethylaminopyridine (DMAP) (14 mg, 0.11 mmol) were added. The reaction mixture was stirred for 1.5 h, whereupon ethanol (0.2 mL) and activated carbon (180 mg) were added. After stirring for 20 h, the reaction was filtered through a plug of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column-chromatography eluting with hexanes/EtOAc (1:1–1:2) to give 175 mg (93%) of **2.36** as a white solid. The ^{1}H NMR spectrum was identical to that previously reported (*vide supra*).



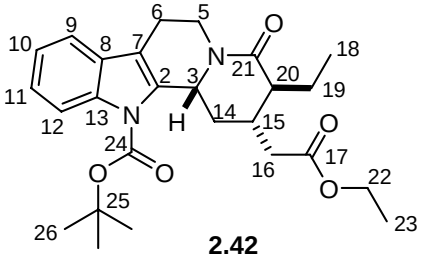
2.32

(3*R, 15*R**)-2-(-4-Oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-2-yl)-[1,3] dithiolane-2-carboxylic acid ethyl ester (2.32) (mp1-303).** A solution of *n*-

BuLi (0.28 mL, 0.67 mmol) in hexanes (2.40 M) was added to a solution of *i*-Pr_2NH (75 mg, 98 μL, 0.74 mmol) in THF (16 mL) at –78 °C. After stirring at –78 °C for 15 min, the flask was transferred to an ice/water bath and stirring was continued for 15 min. The mixture was then recooled to –78 °C. Neat ethyl-1,3-dithiolane-2-carboxylate (180 mg, 0.144 mL, 1.01 mmol) was added, and the resulting solution was stirred at –78 °C for 30 min. A solution of **2.36** (114 mg, 0.336 mmol) in THF (16 mL) at -78 °C was added via cannula. The dry ice/acetone bath was removed, and the reaction was stirred for 3 h at room temperature whereupon NH_4Cl (1.0 mL) was added and 50% of the volatiles were removed under reduced pressure. The mixture was poured into a separatory funnel containing 0.5 M HCl (30 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (1:2 → 1:3) to give 123 mg (71%, *dr* > 95:5) of **2.32** as a white solid: mp 150-151 °C: ^{1}NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.2 Hz, 1 H), 7.42-7.40 (m, 1 H), 7.30-7.27 (m, 1 H), 7.24-7.21 (m, 1 H), 5.16-5.08 (comp, 2 H), 4.23 (app dq, *J* = 7.2, 1.1 Hz, 2 H), 3.38-3.31 (comp, 2 H), 3.30-3.23 (comp, 2 H), 2.97 (ddt, *J* = 11.9, 5.51, 2.6 Hz, 1 H), 2.87-2.81 (comp, 3 H), 2.81-2.65 (comp, 2 H), 2.50 (dd, *J* = 17.5, 11.6 Hz, 1 H), 1.68 (s, 9 H), 1.44-1.37 (m, 1 H), 1.31 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (500 MHz) δ 171.2, 168.7, 150.2, 136.8, 134.7, 128.6, 124.7, 123.0, 118.6, 118.3, 115.5, 84.5, 74.2, 62.5, 54.4, 40.2, 40.0, 39.0, 38.3, 35.8, 33.7, 28.1, 21.6, 13.9; IR (neat) 2974, 2923, 1727, 1640, 1457, 1431, 1411, 1365, 1314, 1222, 1141, 1023, 906, 728 cm^{-1}; mass spectrum (CI) *m/z* 516.1747 [$C_{26}H_{32}N_2O_5S_2$ (M+) requires 516.1753], 237, 289, 339, 362, 391, 517 (base).

NMR Assignments. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.2 Hz, 1 H, C9-H or C12-H), 7.42-7.40 (m, 1 H, C9-H or C12-H), 7.30-7.27 (m, 1 H, C10-H or C11-H),

7.24-7.21 (m, 1 H, C10-H or C11-H), 5.16-5.08 (comp, 2 H, C3-H and C6-H), 4.23 (app dq, *J* = 7.2, 1.1 Hz, 2 H, C21-H), 3.38-3.31 (comp, 2 H, C18-H or C19-H), 3.30-3.23 (comp, 2 H, C18-H or C19-H), 2.97 (ddt, *J* = 11.9, 5.51, 2.6 Hz, 1 H, C15-H**),** 2.87-2.81 (comp, 3 H, C6-H, C14-H, C16-H), 2.81-2.65 (comp, 2H, C5-H), 2.50 (dd, *J* = 17.5, 11.6 Hz, 1 H, C16-H), 1.68 (s, 9 H, C26-H), 1.44-1.37 (m, 1 H, C14-H), 1.20 (t, *J* = 7.2 Hz, 3 H, C20-H); ^{13}C NMR (500 MHz) δ 171.2 (C17), 168.7 (C22), 150.2 (C24), 136.8 (C13), 134.7 (C2), 128.6 (C8), 124.7 (C10 or C11), 123.0 (C10 or C11), 118.6 (C7), 118.3 (C12), 115.5 (C9), 84.5 (C25), 74.2 (C23), 62.5 (C21), 54.4 (C3), 40.2 (C18 or C19), 40.0 (C18 or C19), 39.0 (C6), 38.3 (C15), 35.8 (C16), 33.7 (C14), 28.1 (C26), 21.6 (C5), 13.9 (C20.

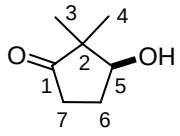


2.42

(3*R, 15*R**, 2*R**)-2-(2-Ethoxycarbonyl-3-ethyl-4-oxo-1,3,4,6,7,12b-hexa hydro-*2H*-indolo [2,3-*α*]quinolizine-12-carboxylic acid *tert*-butyl ester (2.42) (mp2-054, mp2-058).** A solution of sodium hexamethyldisilazide in THF (0.25 mL, 2.0 M, 0.50 mmol) was added dropwise over 7 min to a solution of **2.32** (130 mg, 0.252 mmol) in a mixture of degassed THF (2.3 mL) and toluene (1.0 mL) at -78 °C. The reaction stirred at -78 °C for 1 h, whereupon freshly distilled ethyl iodide (156 mg, 80 μL, 1.00 mmol) was added dropwise. The reaction was stirred at -78 °C for 4 h, whereupon EtOH (0.1 mL) and a saturated aqueous solution of NH_4Cl (1 mL) were added. The cooling bath was removed, the mixture was allowed to warm to room temperature, and the slurry was poured into a separatory funnel containing 0.5 M HCl (10 mL). The resulting aqueous mixture was extracted with EtOAc (3 x 10 mL), and the combined organic layers

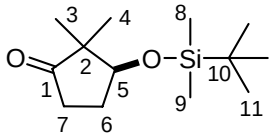
were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with pentane/acetone (2:1) to give a crude oil that was dissolved in EtOH (1.5 mL). Raney Ni (200 mg as a slurry in water) was added, and the reaction was stirred at room temperature for 3 h, whereupon EtOH (3 mL) was added. The reaction was dried (Na_2SO_4), filtered through celite, and the solids were washed with EtOAc (10 mL). The volatiles were removed under reduced pressure, and the resulting residue was purified by flash chromatography eluting with hexanes/EtOAc (1:1) to give 16 mg (20%, *dr* > 95:5) of **2.42** as a colorless oil: ^{1}NMR (500 MHz, $CDCl_3$ δ 8.05 (d, *J* = 7.9 Hz, 1 H), 7.43-7.40 (m, 1 H), 7.30-7.26 (m, 1 H), 7.25-7.20 (m, 1 H), 5.12-5.07 (comp, 2 H), 4.14-4.07 (comp, 2 H), 2.84-2.74 (m, 1 H), 2.73-2.68 (comp, 2 H), 2.66-2.61 (m, 1 H) 2.50 (dd, *J* = 15.4, 3.8 Hz, 1 H), 2.42-2.31 (m, 1 H), 2.22-1.06 (comp, 3 H), 1.80-1.59 (comp, 2 H), 1.68 (s, 9 H), 1.24 (t, *J* = 7.2 Hz, 3 H), 0.93 (t, *J* = 7.5 Hz, 3 H); IR (neat) 2966, 2922, 1732, 1644, 1458, 1414, 1370, 1310, 1157, 751 cm^{-1}; mass spectrum (CI) *m/z* 455.2537 [$C_{26}H_{35}N_2O_5$ (M+1) requires 455.2546], 354, 399, 455 (base), 483.

NMR Assignments. ^{1}NMR (500 MHz, $CDCl_3$ δ 8.05 (d, *J* = 7.9 Hz, 1 H, C9-H or C12-H), 7.43-7.40 (m, 1 H, C9-H, C12-H), 7.30-7.26 (m, 1 H, C10-H, C11-H), 7.25-7.20 (m, 1 H, C10-H, C11-H), 5.12-5.07 (comp, 2 H, C3-H, C6-H), 4.14-4.07 (comp, 2 H, C22-H), 2.84-2.74 (m, 1 H, C6-H), 2.73-2.68 (comp, 2 H, C5-H), 2.66-2.61 (m, 1 H, C16-H) 2.50 (dd, *J* = 15.4, 3.8 Hz, 1 H, C16-H), 2.42-2.31 (m, 1 H, C14-H), 2.22-1.06 (comp, 3 H, C15-H, C19-H, C20-H), 1.80-1.59 (comp, 2 H, C14-H, C19-H), 1.68 (s, 9 H), 1.24 (t, *J* = 7.2 Hz, 3 H, C23-H), 0.93 (t, *J* = 7.5 Hz, 3 H, C18-H).



4.17

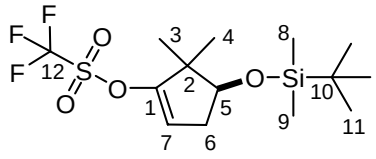
3-Hydroxy-2,2-dimethylcyclopentanone (4.17) (mp2-216). A solution of sucrose (10 g) in water (130 mL) was warmed to 35 ˚C and Baker's yeast (7 g) was added. The mixture was vigorously stirred at 35 ˚C for 15 min, whereupon a solution of **4.16** (650 mg, 5.16 mmol) in water (20 mL) was added. The temperature was reduced to 30 ˚C, and the reaction was stirred overnight. Sucrose (10 g) was added, and the reaction was stirred overnight, whereupon another portion of sucrose (10 g) was added. The mixture was stirred over night whereupon it was filtered through celite and the solids were washed with water (50 mL). The filtrate was saturated with NaCl, extracted with ether (5 x 200 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexanes (2:1) to give 431 mg (65%) of **4.17** as a clear colorless liquid. The ^1H NMR spectrum was identical to that reported previously in the literature.[133]



4.18

3-(*tert*-Butyldimethylsilylanyloxy)-2,2-dimethylcyclpentanone (4.18) (mp-222). TBSCl (2.36 g, 15.7 mmol) was added to a solution of imidazole (2.00 g, 29.5 mmol) and **4.17** (1.18 g, 9.21 mmol) in DMF (18 mL). The solution was stirred at room temperature overnight, whereupon it was poured into a separatory funnel containing saturated aqueous NH_4Cl (40 mL) and water (40 mL). The mixture was extracted with

Et_2O (3 x 40 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with 5% → 10% → 20% Et_2O in pentane to give 1.94 g (87%) of **4.18** as a clear colorless oil. The ^1H NMR spectrum was consistent to that reported previously in the literature.[172]

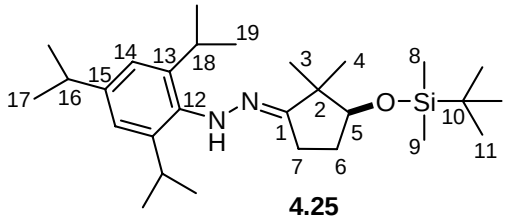


4.19

Trifluoromethanesulfonic acid 4-(*tert*-butyldimethylsilanyloxy)-5,5-dimethyl-cyclopent-1-enyl ester (4.19) (mp2-226). A solution of sodium hexamethyldisilazide (1.24 mmol) in THF (0.620 mL) was added to a solution of **4.18** (200 mg, 0.825 mmol) in THF (8.5 mL) at 0 ˚C. The reaction was stirred at 0 ˚C for 1 h, whereupon a solution of *N*-phenyltriflamide (340 mg, 0.908 mmol) in THF (2.5 mL) was added. The reaction was stirred at 0 ˚C for 1 h, whereupon a saturated aqueous $NaHCO_3$ (10 mL) was added. The mixture was poured into a separatory funnel containing Et_2O (30 mL). The layers were separated, and the organic layer was washed with a saturated aqueous $NaHCO_3$ (15 mL), 50% saturated aqueous NaCl (15 mL), brine (15 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 1% ether in pentane to give 286 mg (93%) of **4.19** as a clear colorless liquid. ^{1}NMR (500 MHz) 5.41 (dd, J = 3.1, 2.2 Hz, 1 H), 3.98 (dd, J = 7.2, 6.7 Hz 1 H) 2.52 (ddd, J = 15.5, 7.2, 3.1 Hz, 1 H), 2.19 (ddd, J = 15.5, 6.7, 2.2 Hz, 1 H) 1.06 (s, 3 H), 1.00 (s, 3 H), 0.88 (s, 9H), 0.05 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (125 MHz) δ 154.0, 109.9, 78.1, 46.3, 35.6, 25.7, 23.6, 18.4, 18.0, -4.6, -4.9; IR (neat) 2957, 2930, 2858, 1651, 1464, 1420,

1249, 1218, 1142, 1064, 838, 601 cm^{-1}; mass spectrum (CI) *m/z* 375.1269 [$C_{14}H_{26}O_4SSiF_3$ (M+1) requires 375.1273], 225, 243, 375 (base).

NMR Assignments. ^{1}NMR (500 MHz) 5.41 (dd, *J* = 3.1, 2.2 Hz, 1 H, C7-H), 3.98 (dd, *J* = 7.2, 6.7 Hz, 1 H, C5-H) 2.52 (ddd, *J* = 15.5, 7.2, 3.1 Hz, 1 H, C6-H), 2.19 (ddd, *J* = 15.5, 6.7, 2.2 Hz, 1 H, C6-H) 1.06 (s, 3 H, C4-H or C3-H), 1.00 (s, 3 H, C4-H or C3-H), 0.88 (s, 9 H, C11-H), 0.05 (s, 3 H, C9-H or C8-H), 0.04 (s, 3 H, C9-H or C8-H); ^{13}C NMR (125 MHz) δ 154.0 (C1), 109.9 (C12 and C7), 78.1 (C5), 46.3 (C2), 35.6 (C6), 25.7 (C11), 23.6 (C4 or C3), 18.4 (C4 or C3), 18.0 (C10), -4.6 (C9 or C8), -4.9 (C9 or C8).

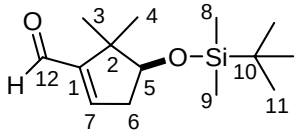


4.25

***N*-[3-(*tert*-Butyldimethylsilanyloxy)-2,2-dimethylcyclopentylidene]-*N*'-(2,4,6-triisopropylphenyl)hydrazine (4.25) (mp2-245).** Trisyl hydrazide (370 mg, 1.237 mmol) was added to a solution of **4.19** (200 mg, 0.825 mmol) in CH_2Cl_2 (5 mL) and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography eluting with 5% → 10% EtOAc in hexanes to give 405 mg (94%) of **4.19** as a white solid; mp 145-147 °C; ^{1}NMR (400 MHz) 7.12 (s, 1 H), 6.94 (s, 1 H, NH), 4.17 (h, *J* = 6.8 Hz, 2 H) 3.69 (app t, *J* = 5.3 Hz, 1 H), 2.87 (h, *J* = 6.8 Hz, 1 H), 2.26 (ddd, *J* = 17.8, 9.2, 5.7 Hz, 1 H), 2.10 (ddd, *J* = 17.8, 9.2, 6.2 Hz, 1 H) 2.00-1.92 (m, 1 H), 1.72-1.64 (m, 1 H), 1.26-1.21 (comp, 18 H), 0.91 (s, 3 H), 0.81 (s, 3 H), 0.79 (s, 9 H) -0.02 (s, 3 H), -0.03 (s, 3 H); IR (neat) 3228, 2959, 2860, 1600, 1462, 1383, 1256, 1165, 1030, 837, 775 cm^{-1}; mass

spectrum (CI) *m/z* 523.3390 [$C_{28}H_{51}N_2O_3SiS$ (M+1) requires 523.3390], 521, 523 (base).

NMR Assignments. ^{1}NMR (400 MHz) 7.12 (s, 1 H, C19-H), 6.94 (s, 1 H, NH), 4.17 (h, *J* = 6.8 Hz, 2 H, C18-H) 3.69 (app t, *J* = 5.3 Hz, 1 H, C5-H), 2.87 (h, *J* = 6.8 Hz, 1 H, C16-H), 2.26 (ddd, *J* = 17.8, 9.2, 5.7 Hz, 1 H, C7-H), 2.10 (ddd, *J* = 17.8, 9.2, 6.2 Hz, 1 H, C7-H), 2.00-1.92 (m, 1 H, C6-H), 1.72-1.64 (m, 1 H), 1.26-1.21 (comp, 18 H, C19-H, C17-H), 0.91 (s, 3 H or C4-H or C3-H), 0.81 (s, 3 H, C4-H or C3-H), 0.79 (s, 9 H, C11-H) -0.02 (s, 3 H,C9- H or C8-H), -0.03 (s, 3 H, C9-H or C8-H).

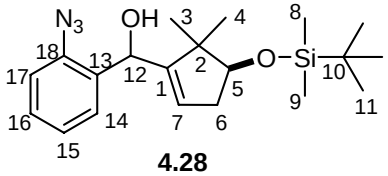


4.26

4-(*tert*-Butyldimethylsilanyloxy)-5,5-dimethylcyclopent-1-enecarbaldehyde (4.26) (mp-234). *n*-BuLi (0.52 mmol) in hexanes (0.22 mL) was added to a solution of **4.25** (100 mg, 0.191 mmol) in hexanes (6.7 mL) containing *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (TMEDA) (0.87 mL) cooled to –78 °C. The reaction was stirred at –78 °C for 25 min, whereupon the cooling bath was replaced with an ice/water bath and stirring continued for 25 min. The reaction was recooled to –78 °C, and a solution of dimethylformamide (42 mg, 44 μL, 0.57 mmol) in TMEDA (0.9 mL) was added. The mixture was stirred at –78 °C for 30 min, whereupon the cold bath was removed and stirring continued 1.5 h at room temperature. A 10% solution of phosphoric acid (3 mL) was added, and the mixture was poured into a separatory funnel containing Et_2O (30 mL) and 10% phosphoric acid (20 mL). The layers were separated, and the organic layer was washed with brine (20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 5%

ether in pentane to give 32 mg (67%) of **4.26** as a clear colorless oil: ^{1}NMR (500 MHz, $CDCl_3$) δ 9.63 (s, 1 H), 6.61 (dd, *J* = 3.1, 2.4 Hz, 1 H), 3.98 (app t, *J* = 6.8 Hz, 1 H), 2.68 (ddd, *J* = 18.5, 6.8, 3.1 Hz, 1 H), 2.34 (ddd, *J* = 18.5, 6.8, 2.4 Hz, 1 H), 1.19 (s, 3 H), 1.06 (s, 3 H), 0.88 (s, 9 H), 0.05 (s, 3 H) 0.04 (s, 3 H); ^{13}C NMR (125 MHz) δ 190.5, 152.6, 149.4, 110.0, 47.0, 40.0, 26.0, 25.0, 19.4, -4.3, -4.7. IR (neat) 2955, 2858, 1687, 1256, 1148, 1124, 883, 837, 776 cm^{-1}; mass spectrum (CI) *m/z* 255.1782 [$C_{14}H_{27}O_2Si$ (M+1) requires 255.1780], 198, (base), 219, 255, 289.

NMR Assignments. ^{1}NMR (500 MHz) δ 9.63 (s, 1 H, C12-H), 6.61 (dd, *J* = 3.1, 2.4 Hz, 1 H, C7-H), 3.98 (app t, *J* = 6.8 Hz, 1 H, C5-H), 2.68 (ddd, *J* = 18.5, 6.8, 3.1 Hz, 1 H, C6-H), 2.34 (ddd, *J* = 18.5, 6.8, 2.4 Hz, 1 H, C6-H), 1.19 (s, 3 H, C3-H or C4-H), 1.06 (s, 3 H, C3-H or C4-H), 0.88 (s, 9 H, C11-H), 0.05 (s, 3 H, C9-H or C8-H) 0.04 (s, 3 H, C9-H or C8-H); ^{13}C NMR (125 MHz) δ 190.5 (C12), 152.6 (C1), 149.4 (C7), 110.0 (C5), 47.0 (C2), 40.0 (C6), 26.0 (C11), 25.0 (C4 and C3), 19.4 (C10), -4.3 (C9 or C8), -4.7 (C9 or C8).



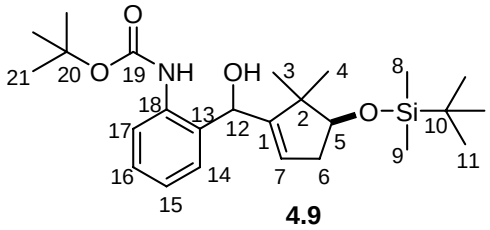
4.28

(2-Azidophenyl)-[3-(*tert*-butyldimethylsilanyloxy)-2,2-dimethylcyclopentyl]-phenylmethanol (4.28) (mp2-267). A solution of *n*-BuLi in hexanes (1.04 mL, 2.37 M, 2.49 mmol) was added to a solution of **4.25** (520 mg, 1.00 mmol) in THF (10 mL) cooled to –78 °C. The reaction was stirred at –78 °C for 30 min, whereupon the cooling bath was replaced with an ice/water bath, and stirring was continued for 10 min. The reaction was recooled to –78 °C, and a solution of *o*-azidobenzaldehyde (439 mg, 2.98 mmol) in THF (7.8 mL + 2.6 mL rinse) was added. The mixture was stirred at –78 °C for 20 min,

whereupon the cold bath was removed, and stirring was continued for 1 h at room temperature. Saturated aqueous NH_4Cl (10 mL) was added, and the mixture was poured into a separatory funnel containing Et_2O (50 mL) and water (5 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (50 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexanes (1:5) to give 287 mg (77%) of **4.28** as a pale yellow oil: ^{1}NMR (500 MHz, mixture of diastereomers) δ 7.45-7.41 (comp, 1 H), 7.32-7.28 (comp, 1 H), 7.14-7.10 (comp, 2 H), 5.44-5.40 (m, 1 H), 5.37-5.35 (m, 0.44 H), 5.28-5.26 (m, 0.56 H), 3.91 (app t, *J* = 6.9 Hz, 0.44 H), 3.86 (app t, *J* = 7.3 Hz, 0.56 H), 2.42-2.32 (comp, 1 H), 2.15-2.08 (comp, 1 H), 2.06-2.00 (comp, 1 H), 1.10 (s, 1.32 H), 1.04 (s, 1.68 H), 0.88-0.86 (comp, 12 H), 0.72 (s, 1.32 H), 0.03-0.01 (comp, 6 H); ^{13}C NMR (125 MHz, mixture of diastereomers) δ 151.8, 151.7, 137.1, 137.0, 133.94, 133.87, 128.9, 128.83, 128.80, 128.7, 128.5, 124.8, 123.0, 122.7, 118.1, 118.0, 81.5, 84.4, 66.9, 66.7, 48.0, 47.8, 37.9, 37.8, 25.82, 25.79, 25.3, 24.6, 20.15, 19.59, 18.08, 18.05, -4.46, -4.48, -4.93, -4.95.

NMR Assignments. ^{1}NMR (500 MHz, mixture of diastereomers) δ 7.45-7.41 (comp, 1 H, Ar-H), 7.32-7.28 (comp, 1 H, Ar-H), 7.14-7.10 (comp, 2 H, Ar-H), 5.44-5.40 (m, 1 H, C12-H), 5.37-5.35 (m, 0.44 H, C7-H), 5.28-5.26 (m, 0.56 H, C7-H), 3.91 (app t, *J* = 6.9 Hz, 0.44 H, C5-H), 3.86 (app t, *J* = 7.3 Hz, 0.56 H, C5-H), 2.42-2.32 (comp, 1 H, C6-H), 2.15-2.08 (comp, 1 H, C6-H), 2.06-2.00 (comp, 1 H, OH), 1.10 (s, 1.32 H, C3-H or C4-H), 1.04 (s, 1.68 H, C3-H or C4-H), 0.88-0.86 (comp, 12 H, C11-H, C3-H or C4-H), 0.72 (s, 1.32 H, C3-H or C4-H), 0.03-0.01 (comp, 6 H, C8-H, C9-H); ^{13}C NMR (125 MHz, mixture of diastereomers) δ 151.8 (C1), 151.7 (C1), 137.1 (Ar-C), 137.0 (Ar-C), 133.94 (Ar-C), 133.87 (Ar-C), 128.9 (Ar-C), 128.83 (Ar-C), 128.80 (Ar-C), 128.7 (Ar-C), 128.5 (Ar-C), 124.8 (Ar-C), 123.0 (C7), 122.7 (C7), 118.1 (Ar-C), 118.0 (Ar-C), 81.5

(C5), 84.4 (C5), 66.9 (C12), 66.7 (C12), 48.0 (C2), 47.8 (C2), 37.9 (C6), 37.8 (C6), 25.82 (C11), 25.79 (C11), 25.3 (C4 or C3), 24.6 (C4 or C3), 20.15 (C4 or C3), 19.59 (C4 or C3), 18.08 (C10), 18.05 (C10), -4.46 (C9 or C8), -4.48 (C9 or C8), -4.93 (C9 or C8), -4.95 (C9 or C8).



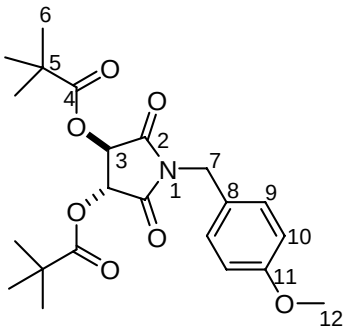
4.9

(2-{[4-tert-Butyldimethylsilanyloxy)-5,5-dimethyl-cyclopent-1-enyl]-hydroxymethyl}-phenyl)-carbamic acid *tert*-butyl ester (4.9) (mp2-268 and mp2-269)

Tributyl phosphine (0.59 mL, 2.35 mmol) was added to a solution of **4.28** (293 mg, 0.78 mmol) in H_2O (0.21 mL) and THF (8 mL). The mixture was stirred at room temperature for 1 h, whereupon it was poured into CH_2Cl_2 (50 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (50 mL) and H_2O (50 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was dissolved in THF (8 mL) and DMAP (10 mg, 0.08 mmol) and Boc_2O (0.5 mL, 2.35 mmol) were added. The reaction was stirred at room temperature for 2 h, whereupon it was poured into a separatory funnel containing Et_2O (50 mL) and 0.5 M HCl (50 mL). The layers were separated and the aqueous layer was extracted with Et_2O (50 mL). The combined organic extracts were, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 10% → 20% Et_2O in hexanes to give 168 mg (48%) of **4.9** as a pale yellow oil: ^{1}NMR (500 MHz, mixture of diastereomers) δ 7.61-7.59 (m, 0.55 H), 7.55-7.52 (m, 0.45 H), 7.37-7.32 (comp, 1 H), 7.20-7.13 (comp, 1.45 H), 7.11-7.09 (m, 0.55 H), 5.64 (d, J = 1.7 Hz, 0.55 H), 5.63 (s, 0.46 H), 5.22-5.20

(m, 0.45 H), 5.11 (app pent, J = 1.7 Hz, 0.55 H), 3.94 (app t, J = 6.2 Hz, 0.45 H), 3.89 (dd, J = 8.0, 7.1 Hz, 0.55 H), 2.42-2.36 (m, 0.45 H), 2.31-2.25 (m, 0.55 H), 2.11-2.03 (m, 1 H), 1.53 (s, 9 H), 1.73 (s, 3 H), 1.08 (s, 1.65 H), 1.01 (s, 1.35 H), 0.88 (s, 4.95 H), 0.87 (s, 4.05 H), 0.04 (s, 4.05 H), 0.01 (s, 4.95 H); ^{13}C NMR (125 MHz, mixture of diastereomers) δ 150.1, 150.0, 149.9, 149.8, 146.6, 145.9, 135.04, 135.01, 128.7, 128.6, 128.1, 128.0, 125.3, 125.2, 125.14, 125.10, 121.8, 121.6, 84.30, 84.29, 81.4, 76.3, 76.2, 48.7, 47.7, 38.4, 37.6, 27.8, 25.8, 24.1, 19.9, 19.4, 18.1, 18.0, -4.49, -4.56, -4.93; IR (neat) 2931, 2857, 1742, 1463, 1369, 1301, 1154 cm^{-1}; mass spectrum (CI) *m/z* 446.2725 [$C_{25}H_{40}O_4Si$ (M-1) requires 446.2727], 372, 429 (base), 446.

NMR Assignments. ^{1}NMR (500 MHz, mixture of diastereomers) δ 7.61-7.59 (m, 0.55 H, Ar-H), 7.55-7.52 (m, 0.45 H, Ar-H), 7.37-7.32 (comp, 1 H, Ar-H), 7.20-7.13 (comp, 1.45 H, Ar-H), 7.11-7.09 (m, 0.55 H, Ar-H), 5.64 (d, J = 1.7 Hz, 0.55 H, C12-H), 5.63 (s, 0.46 H, C12-H), 5.22-5.20 (m, 0.45 H, C7-H), 5.11 (app pent, J = 1.7 Hz, 0.55 H, C7-H), 3.94 (app t, J = 6.2 Hz, 0.45 H, C5-H), 3.89 (dd, J = 8.0, 7.1 Hz, 0.55 H, C5-H), 2.42-2.36 (m, 0.45 H, C6-H), 2.31-2.25 (m, 0.55 H, C6-H), 2.11-2.03 (m, 1 H, C6-H), 1.53 (s, 9 H, C21-H), 1.73 (s, 3 H, C3-H or C4-H), 1.08 (s, 1.65 H, C3-H or C4-H), 1.01 (s, 1.35 H, C3-H or C4-H), 0.88 (s, 4.95 H, C11-H), 0.87 (s, 4.05 H, C11-H), 0.04 (s, 4.05 H, C8-H, C9-H), 0.01 (s, 4.95 H, C8-H, C9-H); ^{13}C NMR (125 MHz, mixture of diastereomers) δ 150.1 (C1), 150.0 (C1), 149.9 (C19), 149.8 (C19), 146.6 (Ar-C), 145.9 (Ar-C), 135.04 (Ar-C), 135.01 (Ar-C), 128.7 (Ar-C), 128.6 (Ar-C), 128.1 (C7), 128.0 (C7), 125.3 (Ar-C), 125.2 (Ar-C), 125.14 (Ar-C), 125.10 (Ar-C), 121.8 (C17 or C14), 121.6 (C17 or C14), 84.30 (C20), 84.29 (C20), 81.4 (C5), 76.3 (C12), 76.2 (C12), 48.7 (C2), 47.7 (C2), 38.4 (C6), 37.6 (C6), 27.8 (C21), 25.8 (C11), 24.1 (C4 or C3), 19.9 (C4 or C3), 19.4 (C4 or C3), 18.1 (C10), 18.0 (C10), -4.49 (C9 or C8), -4.56 (C9 or C8), -4.93 (C9 or C8).

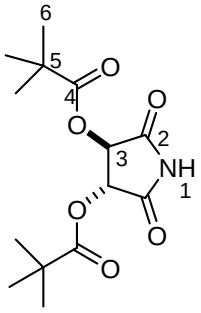


4.38

2,2-Dimethylpropionic acid 4-(2,2-dimethylpropionyloxy)-1-(4-methoxy-benzyl)-2,5-dioxo pyrrolidine-3-yl ester (4.38) (mp2-172). A flask equipped with a Dean-Stark trap was charged with L-tartaric acid (**4.36**) (2.50 g, 16.7 mmol) and 4-methoxybenzyl alcohol (2.40 mL, 18.3 mmol) in xylenes (50 mL) was heated under reflux for 1 h. The mixture was allowed to cool to room temperature. The precipitate was filtered, and the solids were washed with xylenes (50 mL) and Et_2O (30 mL). The solid was dried under high vacuum, and 50% wt of the crude material was dissolved in pyridine (30 mL) and 4-dimethylamino pyridine (DMAP) (10 mg, 0.083 mmol) was added. The mixture was cooled to 0 °C and pivaloyl chloride (5.97 g, 6.10 mL, 49.8 mmol) was added dropwise. The cooling bath was removed, and the reaction was stirred overnight, whereupon it was poured into 1 M HCl (100 mL) and EtOAc (200 mL). The layers were separated, and the organic layer was washed with 1 M HCl (4 x 50 mL), saturated aqueous $NaHCO_3$ (75 mL) and brine (50 mL). The organic layer was dried (Na_2SO_4), and concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (1:9) to give 2.00 g (57%) of **4.38** as a clear colorless oil: ^{1}NMR (500 MHz, $CDCl_3$) δ 7.34-7.31 (m, 2 H), 6.85-6.82 (m, 2 H), 5.48 (s, 2 H), 4.68 (d, *J* = 14.1 Hz, 1 H), 4.61 (d, *J* = 14.1 Hz, 1 H), 3.77 (s, 3 H), 1.23 (s, 18 H); ^{13}C NMR (125 MHz) δ 177.3, 169.3, 159.5, 130.5, 126.9, 114.1, 72.7, 55.3, 42.5,

38.8, 26.9; IR ($CDCl_3$) 2977, 1729, 1514, 1340, 1250, 1154, 1127, 1034 cm^{-1}; mass spectrum (CI) *m/z* 420.2022 [$C_{22}H_{30}NO_7$ (M+1) requires 420.2022], 318, 336, 420, (base), 448.

NMR Assignments. ^{1}NMR (500 MHz) δ 7.34-7.31 (m, 2 H, C9-H), 6.85-6.82 (m, 2 H, C10-H), 5.48 (s, 2 H, C3-H), 4.68 (d, *J* = 14.1 Hz, 1 H, C7-H), 4.61 (d, *J* = 14.1 Hz, 1 H, C7-H), 3.77 (s, 3 H, C12-H), 1.23 (s, 18 H, C6-H); ^{13}C NMR (125 MHz) δ 177.3 (C4), 169.3 (C2), 159.5 (C8), 130.5 (C9), 126.9 (C11), 114.1 (C10), 72.7 (C3), 55.3 (C12), 42.5 (C7), 38.8 (C5), 26.9 (C6).

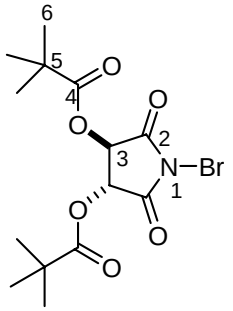


4.39

2,2-Dimethylpropionicacid-4-(2,2-dimethylpropionyloxy)-2,5-dioxopyrrolidin -3-yl ester (4.39) (mp2-174). A solution of ceric ammonium nitrate (4.45 g, 8.11 mmol) in H_2O (40 mL) was added dropwise to a solution of **4.38** (1.62 g, 3.86 mmol) in CH_3CN (40 mL). The cooling bath was removed, and the reaction was stirred at room temperature for 3 h, whereupon brine (75 mL) and EtOAc (75 mL) were added. The mixture was extracted with EtOAc (3 x 75 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (75 mL) and brine (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexanes (6:1 → 4:1) to give 562 mg (49%) of **4.39** as a white solid: mp 163-165 °C ^{1}NMR (500 MHz, $CDCl_3$) δ 8.33 (s, 1 H), 5.48 (s, 2 H),

1.24 (s, 18 H); ^{13}C NMR (125 MHz) δ 177.5, 168.7, 73.4, 38.8, 26.9; IR ($CDCl_3$) 3261, 2975, 1810, 1745, 1218, 1156, 1130, cm^{-1}; mass spectrum (CI) *m/z* 300.1436 [$C_{14}H_{22}NO_6$ (M+1) requires 300.1447], 198, 216, 300, (base), 328, 340.

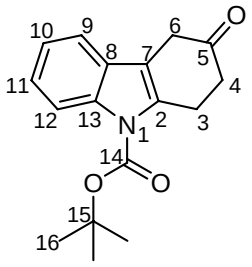
NMR Assignments. ^{1}NMR (500 MHz) δ 8.33 (s, 1 H, NH), 5.48 (s, 2 H, C3-H), 1.24 (s, 18 H, C6-H); ^{13}C NMR (125 MHz) δ 177.5 (C4), 168.7 (C2), 73.4 (C3), 38.8 (C5), 26.9 (C6).



4.40

2,2-Dimethylpropionic acid 1-bromo-4-(2,2-dimethylpropionyloxy)-2,5-dioxopyrrolidin-3-yl ester (4.40) (mp2-203). Sulfuric acid (conc.) (28 μL, 0.50 mmol) was added to a solution of **4.39** (200 mg, 0.668 mmol) in CH_3CO_2H (2 mL) and H_2O (0.4 mL) followed by $NaBrO_3$ (100 mg, 0.663 mmol) and NaBr (69 mg, 0.448 mmol). The reaction was stirred at room temperature for 30 min, whereupon a white precipitate formed. The mixture was diluted with water (2 mL) and filtered. The solid was rinsed with water (2 mL) and dried under high vacuum to afford 226 mg (79%) of **4.40** as a white solid: mp 151-153 °C; ^{1}NMR (500 MHz, $CDCl_3$) δ 5.73 (s, 2 H), 1.24 (s, 18 H); ^{13}C NMR (125 MHz) δ 177.3, 166.6, 72.9, 38.8, 26.8; IR (CH_2Cl_2) 2978, 1750, 1480, 1273, 1121, 763, 716 cm^{-1}; mass spectrum (CI) *m/z* 300.1436 [$C_{14}H_{22}NO_6$ (M+1) requires 300.1447], 198, 216, 300, (base), 328, 340.

NMR Assignments. ^{1}NMR (500 MHz) δ 5.73 (s, 2 H, C3-H), 1.24 (s, 18 H, C6-H); ^{13}C NMR (125 MHz) δ 177.3 (C4), 166.6 (C2), 72.9 (C3), 38.8 (C5), 26.8 (C6).

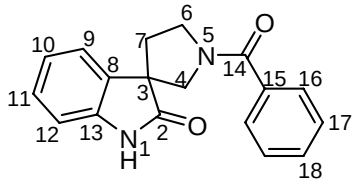


4.46

3-Oxo-1,2,3,4-tetrahydrocarbazole-9-carboxylic acid *tert*-butyl ester (4.46) (mp2-182). DMAP (4 mg, 0.032 mmol) and di-*tert*-butyl dicarbonate (279 mg, 0.27 mL, 1.30 mmol) was added to a solution of **4.45** (60 mg, 0.324 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at room temperature for 3 h, whereupon a saturated NH_4Cl (5 mL) and H_2O (10 mL) were added. The mixture was extracted with EtOAc (3 x 10 mL), and the combined organic fractions were washed with brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexanes (2:1) to give 88 mg (95%) of **4.46** as a white solid: mp 89-91 °C; ^{1}NMR (500 MHz, $CDCl_3$) δ 8.11-8.09 (m, 1 H), 7.34-7.32 (m, 1 H), 7.30-7.27 (m, 1 H), 7.24-7.21 (m, 1 H), 3.52 (t, J = 1.6 Hz, 2 H), 3.47 (tt, J = 6.8 Hz, 1.6, 1 H), 2.77 (t, J = 6.8 Hz, 2 H), 1.66 (s, 9 H) ^{13}C NMR (125 MHz) δ 208.4, 150.4, 136.4, 133.5, 128.4, 124.3, 122.9, 117.5, 115.7, 114.0, 84.1, 39.0, 36.1, 28.3, 25.2; IR (neat) 2976, 1724, 1456, 1359, 1138, 746 cm^{-1}; 285.1368 [$C_{17}H_{19}NO_3$ (M+) requires 285, 1365], 186, 231, 286 (base), 331.

NMR Assignments. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11-8.09 (m, 1 H, C9-H or C12-H), 7.34-7.32 (m, 1 H, C9-H or C12-H) 7.30-7.27 (m, 1 H, C10-H or C11-H) 7.24-7.21 (m, 1 H, C10-H or C11-H), 3.52 (t, J = 1.6 Hz, 2 H, C6-H), 3.47 (tt, J = 6.8 Hz, 1.6,

1 H, C4-H), 2.77 (t, J = 6.8 Hz, 2 H, C3-H), 1.66 (s, 9 H, C16-H) ^{13}C NMR (125 MHz) δ 208.4 (C5), 150.4 (C14), 136.4 (C13), 133.5 (C2), 128.4 (C8), 124.3 (C10 or C11), 122.9 (C10 or C11), 117.5 (C9 or C12), 115.7 (C9 or C12), 114.0 (C7), 84.1 (C15), 39.0 (C3), 36.1 (C6), 28.3 (C16), 25.2 (C4).

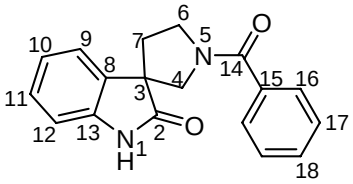


4.52

1'-Benzoyl-1*H*-spiro[indole-3,3'-pyrrolidin]-2-one (4.52) (mp2-206). *N*-Bromosuccinimide (18 mg, 0.11 mmol) was added to a solution of **4.51** (27 mg, 0.098 mmol) in a mixture of THF (0.75 mL), CH_3CO_2H (0.75 mL) and water (0.75 mL) at 0 ˚C. The reaction was stirred at 0 ˚C for 1 h, and the cold bath was removed. Stirring continued for 15 min, whereupon Na_2SO_3 (90 mg) was added followed by saturated aqueous Na_2CO_3 (5 mL) and water (2 mL). The mixture was extracted with CH_2Cl_2 (3 x 5 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexanes (4:1) to give 25.5 mg (89%) of **4.52** as a foam. ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 8.78 (br s, 0.6 H), δ 8.73 (br s, 0.4 H), 7.61 (br s, 0.6 H), 7.52-7.48 (comp, 1.4 H) 7.47-7.29 (comp, 3 H), 7.26-7.00 (comp, 3 H), 6.94-6.87 (m, 1 H), 4.19-3.88 (comp, 3 H, C6-H), 3.83-3.75 (m, 0.4 H), 3.56 (d, J = 10.6 Hz, 0.6 H), 2.59-2.51 (m, 0.6 H), 2.42-2.32 (m, 0.4 H), 2.19-2.12 (m, 1 H).

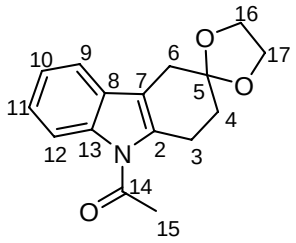
NMR Assignments. ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 8.78 (br s, 0.6 H, NH), δ 8.73 (br s, 0.4 H, NH), 7.61 (br s, 0.6 H, Ar-H), 7.52-7.48 (comp, 1.4 H, Ar-H) 7.47-7.29 (comp, 3 H, Ar-H), 7.26-7.00 (comp, 3 H, Ar-H), 6.94-6.87 (m, 1 H, Ar-H),

4.19-3.88 (comp, 3 H, C6-H, C4-H), 3.83-3.75 (m, 0.4 H, C4-H), 3.56 (d, *J* = 10.6 Hz, 0.6 H, C4-H), 2.59-2.51 (m, 0.6 H, C7-H), 2.42-2.32 (m, 0.4 H, C7-H), 2.19-2.12 (m, 1 H, C7-H).



4.52

1'-Benzoyl-1*H*-spiro[indole-3,3'-pyrrolidin]-2-one (60) (mp2-207). Chiral succinamide **4.40** (41 mg, 0.11 mmol) was added to a solution of **4.51** (27 mg, 0.098 mmol) in a mixture of THF (0.75 mL), CH_3CO_2H (0.75 mL) and water (0.75 mL) at 0 ˚C. The reaction was stirred at 0 ˚C for 1 h, and the cold bath was removed. Stirring continued for 15 min, whereupon Na_2SO_3 (90 mg) was added followed by saturated aqueous Na_2CO_3 (5 mL) and water (2 mL). The mixture was extracted with CH_2Cl_2 (3 x 5 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexanes (4:1) to give 28 mg (94%) of **4.52** as a foam. The ^{1}H NMR spectrum was identical to that previously reported (*vide supra*).

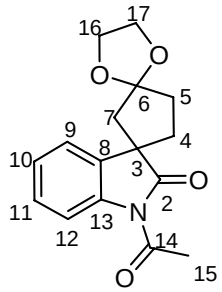


4.56

Indole 4.56 (mp2-293) NaH (60% dispersion in mineral oil, 83 mg, 2.1 mmol) was added to a solution of **4.44** (160 mg, 0.70 mmol) in DMF (7 mL) cooled to 0 °C. The

mixture was stirred for 5 min at 0 °C, whereupon acetyl chloride (220 mg, 0.20 mL, 2.8 mmol) was added. The ice bath was removed and the reaction was stirred 1 h where upon saturated aqueous NH_4Cl (2.0 mL) was added. The mixture was poured into a separatory funnel containing water (40 mL), and was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (1:2) to give 97 mg (36%) of **4.56** as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99-7.96 (m, 1 H, C9-H or C12-H), 7.35-7.33 (m, 1 H, C9-H or C12-H) 7.26-7.19 (comp, 2 H, C10-H, C11-H), 4.07-4.01 (comp, 4 H, C16-H, C17-H), 3.21 (tt, *J* = 6.5, 1.8 Hz, 2 H, C3-H), 2.81 (m, 2 H, C6-H), 2.67 (s, 3 H, C15-H), 2.04 (t, *J* = 6.5 Hz, 2 H, C4-H), ^{13}C NMR (125 MHz) δ 169.7, 136.4, 133.9, 129.8, 124.1, 123.0, 117.7, 116.3, 115.3, 107.9, 64.7, 32.1, 31.9, 37.1, 24.9; IR (neat) 2884, 1697, 1454, 1389, 1312, 1106, 1061, 748 cm^{-1}; mass spectrum (CI) *m/z* 272.1288 [$C_{16}H_{18}NO_3$ (M+1) requires 272.1287], 159 (base), 201, 259, 272.

NMR Assignments. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99-7.96 (m, 1 H, C9-H or C12-H), 7.35-7.33 (m, 1 H, C9-H or C12-H) 7.26-7.19 (comp, 2 H, C10-H, C11-H), 4.07-4.01 (comp, 4 H, C16-H, C17-H), 3.21 (tt, *J* = 6.5, 1.8 Hz, 2 H, C3-H), 2.81 (m, 2 H, C6-H), 2.67 (s, 3 H, C15-H), 2.04 (t, *J* = 6.5 Hz, 2 H, C4-H), ^{13}C NMR (125 MHz) δ 169.7 (C14), 136.4 (C2 or C8 or C13), 133.9 (C2 or C8 or C13), 129.8 (C2 or C8 or C13), 124.1 (C10 or C11), 123.0 (C10 or C11), 117.7 (C9 or C12), 116.3 (C5), 115.3 (C9 or C12), 107.9 (C7), 64.7 (C16, C17), 32.1 (C4), 31.9 (C6), 37.1 (C15), 24.9 (C3).

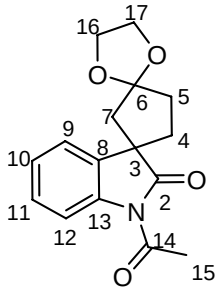


4.57

Spirooxindole 4.57 (mp2-298) A solution of DMDO in acetone (2.9 mL, 0.08 M, 0.23 mmol) was added to a solution of **4.56** (48 mg, 0.18 mmol) in CH_2Cl_2 (2.3 mL) at –78 ˚C. The reaction was stirred at –78 ˚C for 30 min, whereupon the cold bath was removed and the reaction was concentrated under reduced pressure. ^{1}H NMR of the crude reaction mixture indicated that 60% starting material still remained. The crude material was re-dissolved in CH_2Cl_2 (2.3 mL), cooled to –78 ˚C, and a solution of DMDO in acetone (4.4 mL, 0.08 M, 0.35 mmol) was added. The mixture was stirred for 30 min at –78 ˚C, whereupon the cold bath was removed and the reaction was concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexanes (1:2 → 1:1) to give 35 mg (69%) of **4.57** as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19-8.16 (m, 1 H), 7.50-7.47 (m, 1 H), 7.28-7.25 (m, 1 H), 7.21-7.17 (dt, *J* = 7.6, 1.2 Hz, 1 H), 4.04-3.95 (comp, 4 H), 2.66 (s, 3 H), 2.53 (d, *J* = 13.4 Hz, 1 H), 2.34-2.23 (comp, 2 H), 1.13-1.99 (comp, 3 H); ^{13}C NMR (125 MHz) δ 182.3, 171.0, 138.9, 134.7, 128.1, 125.6, 123.0, 117.7, 116.2, 65.0, 64.4, 51.7, 46.9, 37.8, 36.2, 26.6; IR (neat) 2943, 1750, 1710, 1465, 1372, 1343, 1275, 1014, 760 cm^{-1}; mass spectrum (CI) *m/z* 288.1237 [$C_{16}H_{18}NO_4$ (M+1) requires 288.1236], 217, 245, 259, 288 (base).

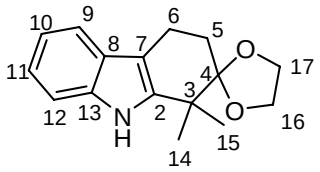
NMR Assignments. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19-8.16 (m, 1 H, C12-H), 7.50-7.47 (m, 1 H, C9-H), 7.28-7.25 (m, 1 H, C10-H), 7.21-7.17 (dt, *J* = 7.6, 1.2 Hz, 1 H,

C11-H), 4.04-3.95 (comp, 4 H, C16-H, C17-H), 2.66 (s, 3 H, C15-H), 2.53 (d, J = 13.4 Hz, 1 H, C7-H), 2.34-2.23 (comp, 2 H, C4-H, C5-H), 1.13-1.99 (comp, 3 H, C4-H, C5-H C7-H); ^{13}C NMR (125 MHz) δ 182.3 (C2), 171.0 (C14), 138.9 (C8 or C13), 134.7 (C8 or C13), 128.1 (C10), 125.6 (C11), 123.0 (C9), 117.7 (C6), 116.2 (C12), 65.0 (C16 or C17), 64.4 (C16 or C17), 51.7 (C3), 46.9 (C7), 37.8 (C4 or C5), 36.2 (C4 or C5), 26.6 (C15).



4.57

Spirooxindole 4.57 (mp2-301). A mixture of oxone (544 mg, 0.89 mmol) and $NaHCO_3$ (230 mg, 2.74 mmol) were added in small portions over 50 min to a solution of **4.56** (48 mg, 0.18 mmol), Bu_4NOH (5 mg, 0.01 mmol) in CH_3CN (2.7 mL) and 1 x 10^{-4} M EDTA (1.8 mL) at 0 °C. Simultaneously, D-epoxone (137 mg, 0.53 mmol) was added in small portions to the reaction mixture over 1 h, whereupon H_2O (8 mL) was added. The mixture was extracted with EtOAc (3 x 10 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc / hexanes (1:2 → 1:1) to give 42 mg (87%) **4.56** and 4 mg (7%) of **4.57** as a clear colorless oil: The ^{1}H NMR spectrum was consistent to that previously reported (*vide supra*).

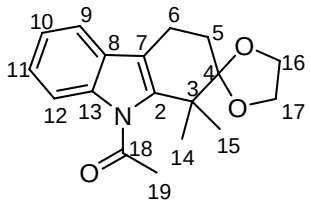


4.65

Indole 4.65 (mp3-155). Phenyl hydrazine (1.04 g, 1.03 mL, 9.61 mmol) was added to a solution of **4.64** (1.61 g, 8.74 mmol) in MeOH (44 mL). The mixture was stirred at room temperature for 40 min, whereupon it was concentration under reduced pressure and the residue was dissolved in EtOAc (100 mL) and washed with H_2O (100 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was co-evaporated with toluene (3 x 30 mL) and dissolved in toluene (55mL) and transferred via cannula to a flask containing freshly fused and powdered $ZnCl_2$ (2.38 g, 17.5 mmol). The mixture was heated to reflux for 4 h, whereupon it was allowed to cool to room temperature and was poured into a separatory funnel containing aqueous saturated $NaHCO_3$ (150 ml). The mixture was extracted with EtOAc (3 x 100 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with Et_2O/pentane (3:7) to give 1.06 g (47% over two steps) of **4.65** as a pale yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (br s, 1H), 7.43 (d, *J* = 7.6 Hz, 1 H), 7.27-7.25 (m, 1 H) 7.11-7.08 (m, 1 H), 7.06-7.03 (m, 1 H), 4.09-3.99 (comp, 4 H), 2.82 (t, *J* = 6.4 Hz, 2 H), 2.04 (t, *J* = 6.4 Hz, 2 H), 1.37 (s, 6 H); ^{13}C NMR (125 MHz) δ 140.5, 136.3, 127.3, 121.2, 119.2, 118.2, 112.4, 110.5, 107.3, 65.3, 40.6, 27.8, 23.9, 18.6; IR (neat) 3414, 2967, 2884, 1460, 1297, 1126, 1096, 743 cm^{-1}; mass spectrum (CI) *m/z* 258.1495 [$C_{16}H_{20}NO_2$ (M+1) requires 258.1494], 171, 196, 257, 258 (base).

NMR Assignments. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (br s, 1H, NH), 7.43 (d, *J* = 7.6 Hz, 1 H, C9-H or C12-H), 7.27-7.25 (m, 1 H, C9-H or C12-H) 7.11-7.08 (m, 1 H,

C10-H or C11-H), 7.06-7.03 (m, 1 H, C10-H or C11-H), 4.09-3.99 (comp, 4 H, C16-H, C17-H), 2.82 (t, J = 6.4 Hz, 2 H, C6-H), 2.04 (t, J = 6.4 Hz, 2 H, C5-H), 1.37 (s, 6 H, C14-H, C15-H); ^{13}C NMR (125 MHz) δ 140.5 (C2 or C8 or C13), 136.3 (C2 or C8 or C13), 127.3 (C2 or C8 or C13), 121.2 (C10 or C11), 119.2 (C10 or C11), 118.2 (C9 or C12), 112.4 (C4), 110.5 (C9 or C12), 107.3 (C7), 65.3 (C16, C17), 40.6 (C3), 27.8 (C5), 23.9 (C14, C15), 18.6 (C6).

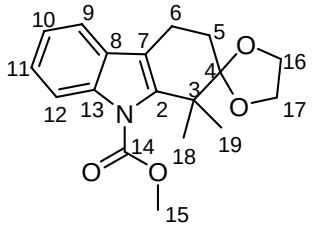


4.66

Indole 4.66 (mp3-126). Freshly powdered NaOH (331 mg, 8.28 mmol) was added to a solution of **4.65** (195 mg, 0.76 mmol) and Bu_4NHSO_4 (28 mg, 0.08 mmol) in CH_2Cl_2 (5.5 mL) cooled to 0 ˚C. The mixture was stirred for 5 min, whereupon acetyl chloride (320 mg, 0.29 mL, 4.1 mmol) was added. The reaction was stirred at 0 ˚C for 30 min, whereupon the ice bath was removed and stirring was continued for 3 h. Saturated aqueous NH_4Cl (2 mL) was added and the mixture was poured into a separatory funnel containing water (15 ml), and extracted with EtOAc (2 x 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with Et_2O/pentane (1:4 → 3:7) to give 71 mg (31%) of **4.66** as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47-7.45 (m, 1 H), 7.41-7.38 (m, 1 H) 7.23-7.19 (m, 1 H), 7.18 (app t, J = 1.0 Hz, 1 H), 4.05-3.99 (comp, 4 H), 2.78 (s, 3 H), 2.77 (t, J = 6.5 Hz, 2 H), 2.07 (t, J = 6.5 Hz, 2 H), 1.45 (s, 6 H); ^{13}C NMR (125 MHz) δ 171.6, 142.6, 136.2, 129.3, 123.6, 122.2, 118.8, 116.5, 113.5, 113.0, 65.3, 43.3, 27.8, 26.0, 21.8, 19.0; IR (neat) 2883, 1713, 1458, 1365, 1295, 1091, 919, 743

cm^{-1}; mass spectrum (CI) *m/z* 299.1518 [$C_{18}H_{21}NO_3$ (M^+) requires 299.1521], 238, 258, 300 (base), 328.

NMR Assignments. ^1H NMR (500 MHz, $CDCl_3$) δ 7.47-7.45 (m, 1 H, C9-H or C12-H), 7.41-7.38 (m, 1 H, C9-H or C12-H) 7.23-7.19 (m, 1 H, C10-H or C11-H), 7.18 (app t, *J* = 1.0 Hz, 1 H, C10-H or C11-H), 4.05-3.99 (comp, 4 H, C16-H, C17-H), 2.78 (s, 3 H, C19-H), 2.77 (t, *J* = 6.5 Hz, 2 H, C6-H), 2.07 (t, *J* = 6.5 Hz, 2 H, C5-H), 1.45 (s, 6 H, C14-H, C15-H); ^{13}C NMR (125 MHz) δ 171.6 (C18), 142.6 (C2 or C8 or C13), 136.2 (C2 or C8 or C13), 129.3 (C2 or C8 or C13), 123.6 (C10 or C11), 122.2 (C10 or C11), 118.8 (C9 or C12), 116.5 (C4), 113.5 (C7), 113.0 (C9 or C12), 65.3 (C16, C17), 43.3 (C3), 27.8 (C19), 26.0 (C5), 21.8 (C14, C15), 19.0 (C6).

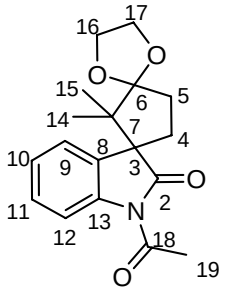


4.67

Indole 4.67 (mp3-120). A solution of sodium hexamethyldisilazide in THF (0.21 mL, 2.0 M, 0.43 mmol) was added to a solution of **4.65** (100 mg, 0.39 mmol) in THF (4 mL) cooled to –78 ˚C. The reaction was stirred at –78 ˚C for 40 min, whereupon methylchloroformate (73 mg, 60 μL, 0.78 mmol) was added. The reaction was stirred at –78 ˚C for 10 min, whereupon the cooling bath was removed, and stirring was continued for 1.5 h. Saturated aqueous NH_4Cl (0.5 mL) was added, and the mixture was poured into a separatory funnel containing 0.5 M HCl (10 ml), and extracted with EtOAc (2 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with

Et_2O/pentane (1:4 → 3:7) to give 114 mg (93%) of **4.67** as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89-7.86 (m, 1 H), 7.38-7.35 (m, 1 H) 7.25-7.16 (comp, 2 H), 4.05-3.99 (comp, 7 H), 2.76 (t, *J* = 6.5 Hz, 2 H), 2.07 (t, *J* = 6.5 Hz, 2 H), 1.53 (s, 6 H); ^{13}C NMR (125 MHz) δ 152.8, 141.1, 137.1, 128.8, 124.0, 122.5, 118.1, 116.8, 114.9, 113.4, 65.2, 53.4, 43.2, 26.0, 21.4, 19.0; IR (neat) 2954, 2884, 1744, 1456, 1358, 1321, 1219, 1092, 1039, 746 cm^{-1}; mass spectrum (CI) *m/z* 316.1537 [$C_{18}H_{22}NO_4$ (M+1) requires 316.1549], 229, 254 (base), 282, 316.

NMR Assignments. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89-7.86 (m, 1 H, C9-H or C12-H), 7.38-7.35 (m, 1 H, C9-H or C12-H) 7.25-7.16 (comp, 2 H, C10-H, C11-H), 4.05-3.99 (comp, 7 H, C15-H, C16-H, C17-H), 2.76 (t, *J* = 6.5 Hz, 2 H, C6-H), 2.07 (t, *J* = 6.5 Hz, 2 H, C5-H), 1.53 (s, 6 H, C18-H, C19-H); ^{13}C NMR (125 MHz) δ 152.8 (C14), 141.1 (C2 or C8 or C13), 137.1 (C2 or C8 or C13), 128.8 (C2 or C8 or C13), 124.0 (C10 or C11), 122.5 (C10 or C11), 118.1 (C9 or C12), 116.8 (C4), 114.9 (C9 or C12), 113.4 (C7), 65.2 (C16, C17), 53.4 (C3), 43.2 (C19), 26.0 (C5), 21.4 (C14, C15), 19.0 (C6).

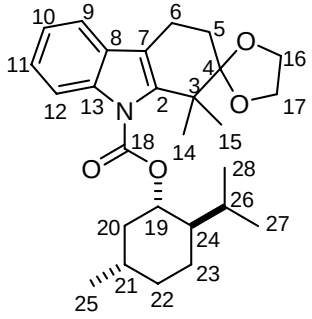


4.68

Spirooxindole 4.68 (mp3-128). D-epoxone (72 mg, 0.28 mmol) was added to a solution of **4.66** (28 mg, 0.09 mmol), Bu_4NHSO_4 (16 mg, 0.05 mmol) and $Na_2B_4O_7{\cdot}H_2O$ (15 mg, 0.05 mmol) in CH_3CN (1.5 mL) and 1 x 10^{-4} M EDTA (1.0 mL). A solution of oxone (305 mg, 0.47 mmol) in 1 x 10^{-4} M EDTA (0.6 mL) and a solution of K_2CO_3 (271

mg, 1.96 mmol) in H_2O (0.9 mL) were added simultaneously in aliquots over 1.5 h. The reaction was stirred at room temperature for an additional 30 min, whereupon it was poured into H_2O (15 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 30% Et_2O in pentane to give 11 mg (40%) of recovered **4.66** and 6 mg (20%) of **4.68** an inseparable mixture: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18-8.15 (m, 1 H), 7.53-7.51 (m, 1 H) 7.27-7.13 (comp, 2 H), 3.98-3.93 (comp, 4 H), 2.63 (s, 3 H), 2.33-2.28 (comp, 2 H), 2.10-2.03 (comp, 2 H), 1.09 (s, 3 H), 0.64 (s, 3 H); mass spectrum (CI) *m/z* 213, 238, 299 (base), 316.

NMR Assignments. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18-8.15 (m, 1 H, C9-H or C12-H), 7.53-7.51 (m, 1 H, C9-H or C12-H) 7.27-7.13 (comp, 2 H, C10-H, C11-H), 3.98-3.93 (comp, 4 H, C16-H, C17-H), 2.63 (s, 3 H, C19-H), 2.33-2.28 (comp, 2 H, C5-H), 2.10-2.03 (comp, 2 H, C4-H), 1.09 (s, 3 H, C14-H or C15-H), 0.64 (s, 3 H, C14-H or C15-H).



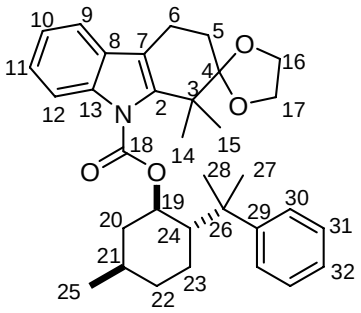
4.71

Indole 4.71 (mp3-135). A solution of sodium hexamethyldisilazide in THF (0.96 mL, 2.0 M, 1.9 mmol) was added to a solution of **4.65** (450 mg, 1.75 mmol) in THF (20 mL) cooled to –78 ˚C. The reaction was stirred at –78 ˚C for 40 min, whereupon menthylchloroformate (763 mg, 0.74 mL, 3.5 mmol) was added dropwise over 5 min.

The reaction was stirred at –78 ˚C for an additional 5 min, whereupon the cooling bath was removed, and stirring was continued for 2 h. Saturated aqueous NH_4Cl (1 mL) was added, and the mixture was poured into a separatory funnel containing 50% saturated aqueous NH_4Cl (10 ml), and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with 5%→10% Et_2O/pentane to give 614 mg (80%) of **4.71** as a white solid: mp 84-87 °C; ^{1}NMR (500 MHz, $CDCl_3$) δ 7.87-7.85 (m, 1 H), 7.37-7.35 (m, 1 H), 7.24-7.19 (m, 1 H), 7.16 (app td, *J* = 7.3, 1.1 Hz, 1 H), 4.98 (app td, *J* = 11.0, 4.4 Hz, 1 H), 4.05-3.95 (comp, 4 H), 2.78-2.74 (comp, 2 H), 2.24-2.19 (m, 1 H), 2.18-2.12 (m, 1 H), 2.05-1.96 (comp, 2 H), 1.78-1.71 (comp, 2 H), 1.67-1.63 (m, 1 H), 1.61 (s, 3 H), 1.59-1.53 (m, 1 H), 1.46 (s, 3 H), 1.28 (app q, *J* = 11.7, Hz, 1 H), 1.18-1.09 (m, 1 H), 1.01-0.92 (m, 1 H), 0.95 (d, *J* = 6.6 Hz, 3 H), 0.89 (d, *J* = 7.0 Hz, 3 H), 0.81 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz) δ 152.1, 141.4, 137.0, 128.8, 123.8, 122.3, 118.1, 116.4, 115.1, 113.5, 77.8, 65.3, 65.2, 47.3, 43.2, 41.2, 34.2, 31.6, 26.3, 26.1, 23.5, 22.9, 22.0, 20.7, 19.7, 19.0, 16.3; IR (neat) 2956, 2873, 1733, 1456, 1369, 1304, 1217, 1092, 1034, 743 cm^{-1}; mass spectrum (CI) *m/z* 439.2720 [$C_{27}H_{37}NO_4$ (M^+) requires 439.2723], 302, 378, 438, 440 (base).

NMR Assignments. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87-7.85 (m, 1 H, C9-H or C12-H), 7.37-7.35 (m, 1 H, C9-H or C12-H), 7.24-7.19 (m, 1 H, C10-H or C11-H), 7.16 (app td, *J* = 7.3, 1.1 Hz, 1 H, C10-H or C11-H), 4.98 (app td, *J* = 11.0, 4.4 Hz, 1 H, C19-H), 4.05-3.95 (comp, 4 H, C16-H, C17-H), 2.78-2.74 (comp, 2 H, C6-H), 2.24-2.19 (m, 1 H, C20-H), 2.18-2.12 (m, 1 H, C5-H), 2.05-1.96 (comp, 2 H, C5-H, C26-H), 1.78-1.71 (comp, 2 H, C22-H, C23-H), 1.67-1.63 (m, 1 H, C24-H), 1.61 (s, 3 H, C14-H or C15-H), 1.59-1.53 (m, 1 H, C21-H), 1.46 (s, 3 H, C14-H or C15-H), 1.28 (app q, *J* = 11.7, Hz, 1 H, C20-H), 1.18-1.09 (m, 1 H, C23-H), 1.01-0.92 (m, 1 H, C22-H), 0.95 (d, *J* = 6.6 Hz, 3

H, C25-H), 0.89 (d, J = 7.0 Hz, 3 H, C27-H or C28-H), 0.81 (d, J = 7.0 Hz, 3 H, C27-H or C28-H); ^{13}C NMR (125 MHz) δ 152.1 (C18), 141.4 (C2 or C8 or C13), 137.0 (C2 or C8 or C13), 128.8 (C2 or C8 or C13), 123.8 (C10 or C11), 122.3 (C10 or C11), 118.1 (C9 or C12), 116.4 (C4), 115.1 (C9 or C12), 113.5 (C7), 77.8 (C19), 65.3 (C16 or C17), 65.2 (C16 or C17), 47.3 (C24), 43.2 (C3), 41.2 (C20), 34.2 (C22), 31.6 (C21), 26.3 (C26), 26.1 (C5), 23.5 (C23), 22.9 (C14 or C15), 22.0 (C25), 20.7 (C27 or C28), 19.7 (C14 or C15), 19.0 (C6), 16.3 (C27 or C28).



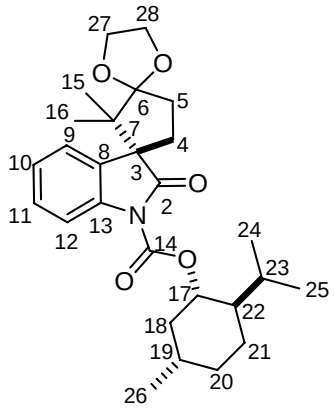
4.72

Indole 4.72 (mp3-144). A solution of sodium hexamethyldisilazide in THF (0.30 mL, 2.0 M, 0.60 mmol) was added to a solution of **4.65** (140 mg, 0.54 mmol) in THF (2.75 mL) cooled to –78 ˚C. The reaction was stirred at –78 ˚C for 45 min, whereupon a solution of 8-phenylmenthyl chloroformate (241 mg, 0.82 mmol) in THF (0.4 mL) was added dropwise over 5 min. The reaction was stirred at –78 ˚C for an additional 15 min, whereupon the cooling bath was removed, and stirring was continued for 1.5 h. A solution of 0.5 M HCl (1 mL) was added, and the mixture was poured into a separatory funnel containing 0.5 M HCl (8 mL), EtOAc (8 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 8 mL). The combined organic extracts were dried (Na_2SO_4), and concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with 20% Et_2O/pentane to give 176 mg (63%) of **4.72** as

a pale yellow foam; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76-7.73 (m, 1 H), 7.35-7.33 (m, 1 H), 7.24-7.20 (comp, 2 H), 7.19-7.14 (comp, 2 H), 7.09-7.05 (comp, 2H), 6.93-6.89 (m, 1 H), 5.09 (app td, *J* = 11.0, 4.4 Hz, 1 H), 4.10-3.94 (comp, 4 H), 2.77-2.74 (comp, 2 H), 2.24-2.11 (comp, 3 H), 1.92 (app td, *J* = 13.2, 4.4 Hz, 1 H), 1.67 (s, 3H), 1.64-1.59 (m, 1 H), 1.58-1.47 (comp, 2 H), 1.45 (s, 3 H), 1.34 (s, 3 H), 1.33 (s, 3 H), 1.27 (app q, *J* = 11.9 Hz, 1 H), 1.08 (qd, *J* = 13.2, 3.4 Hz, 1 H), 0.94-0.85 (m, 1 H) 0.89 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz) δ 151.5, 150.3, 141.3, 137.0, 128.8, 127.9, 125.5, 125.1, 123.7, 122.2, 117.9, 116.7, 115.3, 113.5, 78.3, 65.3, 65.1, 51.3, 43.2, 42.2, 40.2, 34.5, 31.6, 28.5, 27.2, 26.1, 25.3, 24.4, 21.7, 19.0, 18.5; IR (neat) 2956, 1731, 1456, 1364, 1217, 1092, 1034, 920, 735 cm^{-1}; mass spectrum (CI) *m/z* 515.3033 [$C_{33}H_{41}NO_4$ (M^+) requires 515.3036], 302, 515 (base), 557, 620.

NMR Assignments. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76-7.73 (m, 1 H, C9-H or C12-H), 7.35-7.33 (m, 1 H, C9-H or C12-H), 7.24-7.20 (comp, 2 H, Ar-H), 7.19-7.14 (comp, 2 H, C10-H, C11-H), 7.09-7.05 (comp, 2H, Ar-H), 6.93-6.89 (m, 1 H, Ar-H), 5.09 (app td, *J* = 11.0, 4.4 Hz, 1 H, C19-H), 4.10-3.94 (comp, 4 H, C16-H, C17-H), 2.77-2.74 (comp, 2 H, C6-H), 2.24-2.11 (comp, 3 H, C5-H, C20-H, C24-H), 1.92 (app td, *J* = 13.2, 4.4 Hz, 1 H, C5-H), 1.67 (s, 3H, C14-H or C15-H), 1.64-1.59 (m, 1 H, C22-H), 1.58-1.47 (comp, 2 H, C21-H, C23-H), 1.45 (s, 3 H, C14-H or C-15), 1.34 (s, 3 H, C27-H or C28-H), 1.33 (s, 3 H, C27-H or C28-H), 1.27 (app q, *J* = 11.9 Hz, 1 H, C20-H), 1.08 (qd, *J* = 13.2, 3.4 Hz, 1 H, C23-H), 0.94-0.85 (m, 1 H, C22-H) 0.89 (d, *J* = 6.6 Hz, 3 H, C25-H); ^{13}C NMR (125 MHz) δ 151.5 (C18), 150.3 (C29), 141.3 (C2 or C8 or C13), 137.0 (C2 or C8 or C13), 128.8 (C2 or C8 or C13), 127.9 (Ar-C), 125.5 (Ar-C), 125.1 (Ar-C), 123.7 (C10 or C11), 122.2 (C10 or C11), 117.9 (C9 or C12), 116.7 (C4), 115.3 (C9 or C12), 113.5 (C7), 78.3 (C19), 65.3 (C16 or C17), 65.1 (C16 or C17), 51.3 (C24), 43.2 (C3),

42.2 (C20), 40.2 (C26), 34.5 (22), 31.6 (C21), 28.5 (C27 or C28), 27.2 (C23), 26.1 (C5), 25.3 (C27 or C28), 24.4 (C14 or C15), 21.7 (C25), 19.0 (C6), 18.5 (C14 or C15).

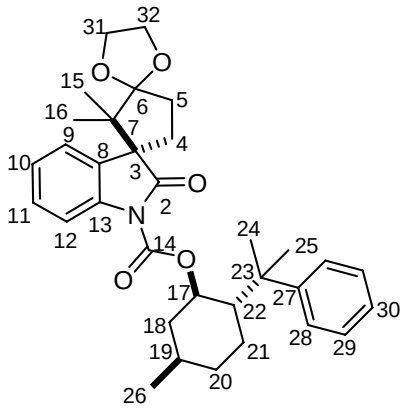


4.75

Spirooxindole 4.75 (mp4-260). A solution of DMDO in acetone (3.3 mL, 0.08 M, 0.26 mmol) was added to a solution of **4.71** (50 mg, 0.11 mmol) in acetone (2 mL) at 0 ˚C. The reaction was stirred at 0 ˚C for 1 h and then concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (4 mL), and silica gel (400 mg) was added. The slurry was stirred at room temperature for 3.5 h, whereupon it was filtered through celite. The solids were washed with EtOAc (10 mL), and the filtrate and washings were removed under reduced pressure. The residue was purified by flash chromatography eluting with hexanes / EtOAc (4:1) to give 41 mg (78%, dr = 2:1) of **4.75** as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.82-7.79 (comp, 1 H), 7.56-7.53 (comp, 1 H), 7.25-7.21 (comp, 1 H), 7.12-7.08 (comp, 1 H), 4.90-4.83 (comp, 1 H), 4.01-3.88 (comp, 4 H), 2.37-2.23 (comp, 2 H), 2.20-1.09 (comp, 2 H), 2.04-1.93 (comp, 3 H), 1.74-1.67 (comp, 2 H), 1.63-1.48 (comp, 2 H), 1.19-1.12 (comp, 1 H), 1.13 (s, 2H), 1.12 (s, 1H), 0.95-0.86 (comp, 2 H), 0.99-0.89 (comp, 6 H), 0.79 (d, *J* = 6.8 Hz, 3 H), 0.78 (d, *J* = 6.8 Hz, 3 H), 0.60 (s, 1 H), 0.59 (s, 2 H); ^{13}C

NMR (125 MHz) δ 178.5, 178.4, 150.8, 150.7, 139.09, 139.06, 132.7, 132.5, 127.70, 127.67, 126.2, 125.5, 123.7, 123.6, 119.1, 114.09, 114.05, 77.7, 77.6, 65.2, 64.1, 59.2, 59.1, 50.9, 46.9, 46.8, 40.8, 40.7, 34.1, 33.7, 33.6, 31.53, 31.50, 31.0, 26.5, 25.9, 23.7, 23.5, 23.3, 23.2, 21.98, 21.96, 20.9, 20.7, 20.3, 20.2, 16.6, 16.1. IR (neat) 2955, 2872, 1766, 1725, 1467, 1356, 1290, 1242, 1150 cm^{-1}; mass spectrum (CI) *m/z* 456.2748 [$C_{27}H_{38}NO_5$ (M+1) requires 456.2750], 274, 318, 456 (base).

NMR Assignments. ^1H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.82-7.79 (comp, 1 H, C9-H or C12-H), 7.56-7.53 (comp, 1 H, C9-H or C12-H), 7.25-7.21 (comp, 1 H, C10-H or C11-H), 7.12-7.08 (comp, 1 H, C10-H or C11-H), 4.90-4.83 (comp, 1 H, 17-H), 4.01-3.88 (comp, 4 H, C27-H, C28-H), 2.37-2.23 (comp, 2 H, C4-H, C5-H), 2.20-1.09 (comp, 2 H, C18-H, C23-H), 2.04-1.93 (comp, 3 H, C4-H, C5-H, C23-H), 1.74-1.67 (comp, 2 H, C20-H, C21-H), 1.63-1.48 (comp, 2 H, C19-H, C22-H), 1.19-1.12 (comp, 1 H, C18-H), 1.13 (s, 2H, C15-H or C16-H), 1.12 (s, 1H, C15-H or C16-H), 0.95-0.86 (comp, 2 H, C20-H, C21-H), 0.99-0.89 (comp, 6 H, C24-H, C25-H or C26-H), 0.79 (d, J = 6.8 Hz, 3 H, C24 or C25), 0.78 (d, J = 6.8 Hz, 3 H, C24 or C25), 0.60 (s, 1 H, C15-H or C16-H), 0.59 (s, 2 H, C15-H or C16-H); ^{13}C NMR (125 MHz) δ 178.5 (C2), 178.4 (C2), 150.8 (C14), 150.7 (C14), 139.09 (C13), 139.06 (C13), 132.7 (C8), 132.5 (C8), 127.70 (C10 or C11), 127.67 (C10 or C11), 126.2 (C9 or C12), 125.5 (C28), 123.7 (C10 or C11), 123.6 (C10 or C11), 119.1 (C6), 114.09 (C9 or C12), 114.05 (C9 or C12), 77.7 (C17), 77.6 (C17), 65.2 (C27 or C28), 64.1 (C27 or C28), 59.2 (C3), 59.1 (C3), 50.9 (C7), 46.9 (C22), 46.8 (C22), 40.8 (C18), 40.7 (C18), 34.1 (C20), 33.7 (C4 or C5), 33.6 (C4 or C5), 31.53 (C19), 31.50 (C4 or C5), 31.0 (C4 or C5), 26.5 (C23), 25.9 (C23), 23.7 (C21), 23.5 (C15 or C16), 23.3 (C21), 23.2 (C15 or C16), 21.98 (C24 or C25), 21.96 (C24 or C25), 20.9 (C26), 20.7 (C26), 20.3 (C15 or C16), 20.2 (C15 or C16), 16.6 (C24 or C25), 16.1 (C24 or C25).

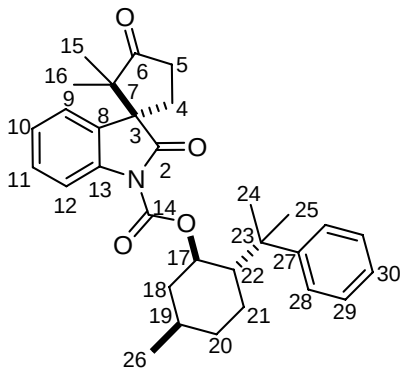


4.76

Spirooxindole 4.76 (mp4-259). A solution of DMDO in acetone (2.5 mL, 0.08 M, 0.20 mmol) was added to a solution of **4.72** (45 mg, 0.09 mmol) in acetone (1.5 mL) at 0 ˚C. The reaction was stirred at 0 ˚C for 1 h and then concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (3 mL), and silica gel (300 mg) was added. The slurry was stirred at room temperature for 3.5 h, whereupon it was filtered through celite. The solids were washed with EtOAc (10 mL), and the combined filtrate and washings were removed under reduced pressure. The residue was purified by flash chromatography eluting with hexanes / EtOAc (4:1) to give 36 mg (78%, dr = 12:1) of **4.76** as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68-7.65 (m, 1 H), 7.54-7.51 (m, 1 H), 7.25 (dd, *J* = 8.5, 1.2 Hz, 2 H), 7.23-7.19 (m, 1 H), 7.10 (td, *J* = 7.5, 1.2 Hz, 1 H), 7.07-7.03 (comp, 2H), 6.88 (tt, *J* = 7.4, 1.0 Hz, 1 H), 5.09 (td, *J* = 10.6, 4.6 Hz, 1 H), 3.99-3.88 (comp, 4 H), 2.31-2.24 (comp, 2 H), 2.14 (ddd, *J* = 12.3, 10.6, 3.4 Hz, 1 H), 2.01-1.96 (comp, 3 H), 1.65-1.57 (comp, 2 H), 1.51-1.42 (m, 1 H), 1.36 (s, 3H), 1.28 (s, 3H), 1.26-1.18 (m, 1 H), 1.13-1.56 (m, 1 H), 1.09 (s, 3 H), 0.91-0.82 (m, 1 H), 0.87 (d, *J* = 6.6 Hz, 3 H), 0.56 (s, 3 H); ^{13}C NMR (125 MHz) δ 177.5, 150.7, 150.0, 139.1, 132.4, 127.8, 127.5, 126.1, 125.5, 125.0, 123.5, 119.1, 114.2, 65.2, 64.8, 58.9, 50.9, 50.6, 41.9,

40.0, 34.3, 33.6, 31.45, 31.38, 26.8, 26.64, 26.57, 23.4, 21.7, 20.4; IR (neat) 2955, 2882, 1766, 1721, 1478, 1465, 1358, 1292, 1243, 1149 $^{cm-1}$; mass spectrum (CI) *m/z* 531.2978 [$C_{33}H_{41}NO_5$ (M^+) requires 531.2985], 274, (base), 516, 532.

NMR Assignments. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68-7.65 (m, 1 H, C9-H or C12-H), 7.54-7.51 (m, 1 H, C9-H or C12-H), 7.25 (dd, *J* = 8.5, 1.2 Hz, 2 H, C28), 7.23-7.19 (m, 1 H, C10-H or C11-H), 7.10 (td, *J* = 7.5, 1.2 Hz, 1 H, C10-H or C11-H), 7.07-7.03 (comp, 2H, C29-H), 6.88 (tt, *J* = 7.4, 1.0 Hz, 1 H, C30-H), 5.09 (td, *J* = 10.6, 4.6 Hz, 1 H, C17-H), 3.99-3.88 (comp, 4 H, C31-H, C32-H), 2.31-2.24 (comp, 2 H, C4-H, C5-H), 2.14 (ddd, *J* = 12.3, 10.6, 3.4 Hz, 1 H, C22-H), 2.01-1.96 (comp, 3 H, C18-H, C5-H C4-H), 1.65-1.57 (comp, 2 H, C20-H, C21-H), 1.51-1.42 (m, 1 H, C19-H), 1.36 (s, 3H, C24-H or C25-H), 1.28 (s, 3H, C15-H or C16-H), 1.26-1.18 (m, 1 H, C18-H), 1.13-1.56 (m, 1 H, C21-H), 1.09 (s, 3 H, C24-H or C-25), 0.91-0.82 (m, 1 H, C20-H), 0.87 (d, *J* = 6.6 Hz, 3 H, C26-H), 0.56 (s, 3 H, C15-H or C16-H); ^{13}C NMR (125 MHz) δ 177.5 (C2), 150.7 (C14), 150.0 (C27), 139.1 (C13), 132.4 (C8), 127.8 (C29), 127.5 (C10 or C11), 126.1 (C9 or C12), 125.5 (C28), 125.0 (C30), 123.5 (C10 or C11), 119.1 (C6), 114.2 (C9 or C12), 65.2 (C31 or C32), 64.8 (C31 or C32), 58.9 (C3), 50.9 (C7), 50.6 (C22), 41.9 (C18), 40.0 (C23), 34.3 (C20), 33.6 (C4 or C5), 31.45 (C4 or C5), 31.38 (C19), 26.8 (C21), 26.64 (C15 or C16), 26.57 (C24 or C25), 23.4 (C24 or C25), 21.7 (C26), 20.4 (C15 or C16).

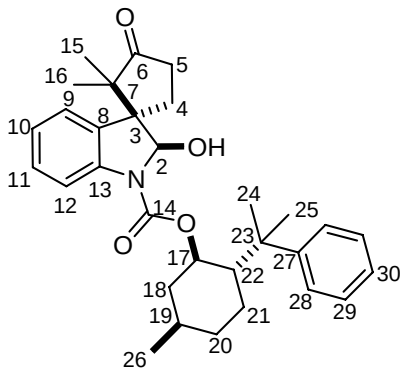


4.77

Ketone 4.77 (mp5-072, mp5-073, mp5-074). A solution of DMDO in acetone (58 mL, 0.08 M, 4.64 mmol) was added to a solution of **4.72** (1.00 g, 1.94 mmol) in acetone (34 mL) at 0 ˚C. The reaction was stirred at 0 ˚C for 1.25 h and then concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (60 mL), and silica gel (6.6 g) was added. The slurry was stirred at room temperature for 3.5 h, whereupon it was filtered through celite. The solids were washed with EtOAc (100 mL), and the combined filtrate and washings were removed under reduced pressure. The residue was dissolved in acetone (50 mL) and $TsOH{\cdot}H_2O$ (369 mg, 1.94 mmol) was added. The reaction was heated under reflux for 1 h, whereupon it was allowed to cool to room temperature. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with hexanes / EtOAc (4:1 → 3:1) to give 692 mg (73%, dr = 12:1) of **4.77** as a white foam; $[\alpha]_D$ –62.5 (CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78-7.76 (m, 1 H), 7.33 (ddd, *J* = 8.2, 5.6, 3.2 Hz, 1 H), 7.26-7.23 (comp, 2 H), 7.18-7.16 (comp, 2 H), 7.05-7.01 (comp, 2H), 6.88-6.84 (m, 1 H), 5.08 (td, *J* = 10.8, 4.6 Hz, 1 H), 2.84 (dt, *J* = 19.4, 9.8 Hz, 1 H), 2.55 (ddd, *J* = 19.4, 8.6, 4.4 Hz, 1 H), 2.27-2.22 (comp, 2 H), 2.17 (ddd, *J* = 12.5, 10.8, 3.6 Hz, 1 H), 1.96- 1.91 (m, 1 H), 1.74 (dq, *J* = 13.6, 3.6 Hz, 1 H), 1.66-1.60 (m, 1 H), 1.52-1.43 (m, 1 H), 1.35 (s, 3H), 1.26-1.21 (m, 1 H), 1.25

(s, 3 H), 1.18-1.09 (m, 1 H), 1.06 (s, 3 H), 0.93-0.85 (m, 1 H), 0.87 (d, J = 6.6 Hz, 3 H), 0.82 (s, 3 H); ^{13}C NMR (125 MHz) δ 218.0, 177.1, 151.0, 150.0, 140.0, 128.7, 127.8, 127.4, 125.4, 124.9, 124.4, 124.1, 115.1, 77.5, 57.9, 53.1, 50.5, 41.7, 39.8, 34.2, 33.2, 31.4, 28.3, 27.8, 26.6, 25.0, 21.7, 21.3, 17.9. IR (neat) 2965, 1760, 1745, 1725, 1464, 1357, 1293, 1244, 1163 cm^{-1}; mass spectrum (CI) *m/z* 487.2720 [$C_{31}H_{37}NO_4$ (M^+) requires 487.2723], 267, 488 (base).

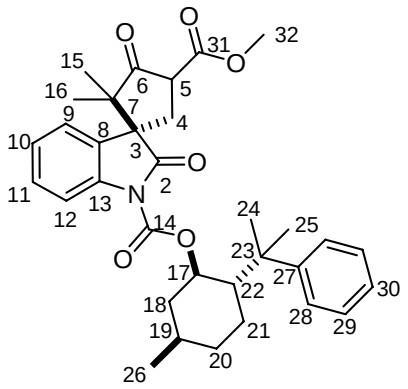
NMR Assignments. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78-7.76 (m, 1 H, C9-H or C12-H), 7.33 (ddd, J = 8.2, 5.6, 3.2 Hz, 1 H, C10-H or C11-H), 7.26-7.23 (comp, 2 H, C28-H), 7.18-7.16 (comp, 2 H, C10-H or C11-H, C9-H or C12-H), 7.05-7.01 (comp, 2H, C29-H), 6.88-6.84 (m, 1 H, C30-H), 5.08 (td, J = 10.8, 4.6 Hz, 1 H, C17-H), 2.84 (dt, J = 19.4, 9.8 Hz, 1 H, C5-H), 2.55 (ddd, J = 19.4, 8.6, 4.4 Hz, 1 H, C5-H), 2.27-2.22 (comp, 2 H, C4-H), 2.17 (ddd, J = 12.5, 10.8, 3.6 Hz, 1 H, C22-H), 1.96- 1.91 (m, 1 H, C18-H), 1.74 (dq, J = 13.6, 3.6 Hz, 1 H, C21-H), 1.66-1.60 (m, 1 H, C20-H), 1.52-1.43 (m, 1 H, C19-H), 1.35 (s, 3H, C24-H or C25-H), 1.26-1.21 (m, 1 H, C18-H), 1.25 (s, 3 H, C15-H or C-16), 1.18-1.09 (m, 1 H, C21-H), 1.06 (s, 3 H, C24-H or C25-H), 0.93-0.85 (m, 1 H, C20-H), 0.87 (d, J = 6.6 Hz, 3 H, C26-H), 0.82 (s, 3 H, C15-H or C16-H); ^{13}C NMR (125 MHz) δ 218.0 (C6), 177.1 (C2), 151.0 (C14), 150.0 (C27), 140.0 (C13), 128.7 (C10 or C11), 127.8 (C29), 127.4 (C8), 125.4 (C28), 124.9 (C30), 124.4 (C10 or C11), 124.1 (C9 or C12), 115.1 (C9 or C12), 77.5 (C17), 57.9 (C3), 53.1 (C7), 50.5 (C22), 41.7 (C18), 39.8 (C23), 34.2 (C20), 33.2 (5), 31.4 (C19), 28.3 (C4), 27.8 (C15 or C16), 26.6 (C21), 25.0 (C24 or C25), 21.7 (C26), 21.3 (C24 or C25), 17.9 (C15 or C16).



4.78

Ketone 4.78 (mp4-091). $NaBH_4$ (5 mg, 0.12 mmol) was added to a solution of **4.77** (40 mg, 0.08 mmol) in MeOH (0.4 mL) at 0 °C. The reaction was stirred at 0 °C for 15 min, whereupon a saturated aqueous solution of NH_4Cl (2 mL) was added. The ice bath was removed and the mixture was stirred for 3 min, whereupon it was poured in H_2O (10 mL). The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic phases were dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with hexanes / EtOAc (4:1) to give 28 mg (69%) of **4.78** as a white solid; ^{1}H NMR (500 MHz, DMSO d_6, 100 ˚C) δ 7.69 (d, *J* = 6.8, Hz, 1 H), 7.34 (dd, *J* = 8.5, 1.1 Hz, 2 H), 7.26-7.22 (comp, 2 H), 7.17 (td, *J* = 7.5, 1.3 Hz, 1 H), 7.13-7.10 (m, 1 H), 6.91 (td, *J* = 7.5, 1.1 Hz, 1 H), 6.68 (d, *J* = 7.5, Hz, 1 H), 5.21 (br s), 4.89 (td, *J* = 10.6, 4.5 Hz, 1 H), 2.52-2.44 (m, 1 H), 2.25-2.13 (comp, 3 H), 1.93-1.88 (m, 1 H), 1.61-1.57 (m, 1 H), 1.56-1.50 (m, 1 H), 1.49-1.35 (comp, 2 H, C6-H), 1.36 (s, 3H), 1.26 (s, 3H), 1.28-1.23 (m, 1 H), 1.22 (s, 3 H), 1.11-1.03 (m, 1 H), 1.10 (s, 3 H), 0.89-0.81 (m, 1 H), 0.87 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO d_6, 100 ˚C) δ 219.4, 151.2, 150.5, 139.9, 134.2, 127.3, 126.8, 124.9, 124.6, 122.9, 121.4, 114.5, 89.4, 75.0, 57.2, 49.2, 48.9, 41.0, 33.7, 32.3, 31.3, 30.4, 26.7, 26.1, 25.1, 21.1, 20.2, 19.1.

NMR Assignments. ^{1}H NMR (500 MHz, DMSO d_6, 100 ˚C) δ 7.69 (d, *J* = 6.8, Hz, 1 H, C9-H or C12-H), 7.34 (dd, *J* = 8.5, 1.1 Hz, 2 H, C28-H), 7.26-7.22 (comp, 2 H, C29-H), 7.17 (td, *J* = 7.5, 1.3 Hz, 1 H, C10-H or C11-H), 7.13-7.10 (m, 1 H, C30-H), 6.91 (td, *J* = 7.5, 1.1 Hz, 1 H, C10-H or C11-H), 6.68 (d, *J* = 7.5, Hz, 1 H, C9-H or C12-H), 5.21 (br s, 1 H, C2-H), 4.89 (td, *J* = 10.6, 4.5 Hz, 1 H, C17-H), 2.52-2.44 (m, 1 H, C5-H), 2.25-2.13 (comp, 3 H C5-H, C6-H, C22-H), 1.93-1.88 (m, 1 H, C18-H), 1.61-1.57 (m, 1 H, C20-H), 1.56-1.50 (m, 1 H, C21-H), 1.49-1.35 (comp, 2 H, C6-H, C19-H), 1.36 (s, 3H, C15-H or C16-H), 1.26 (s, 3H, C15-H or C16-H), 1.28-1.23 (m, 1 H, C18-H), 1.22 (s, 3 H, C24-H or C-25), 1.11-1.03 (m, 1 H, C21-H), 1.10 (s, 3 H, C24-H or C25-H), 0.89-0.81 (m, 1 H, C20-H), 0.87 (d, *J* = 6.5 Hz, 3 H, C26-H); ^{13}C NMR (125 MHz, DMSO d_6, 100 ˚C) δ 219.4 (C6), 151.2 (C14), 150.5 (C27), 139.9 (C13), 134.2 (C8), 127.3 (C29), 126.8 (C10 or C11), 124.9 (C28), 124.6 (30), 122.9 (C9 or C12), 121.4 (C10 or C11), 114.5 (C9 or C12), 89.4 (C2), 75.0 (C17), 57.2 (C3 or C7), 49.2 (C3 or C7), 48.9 (C22), 41.0 (C18), 33.7 (C20), 32.3 (C5), 31.3 (C6), 30.4 (C19), 26.7 (C15 or C16), 26.1 (C21), 25.1 (C15 or C16), 21.1 (C26), 20.2 (C24 or C25), 19.1 (C24 or C25).



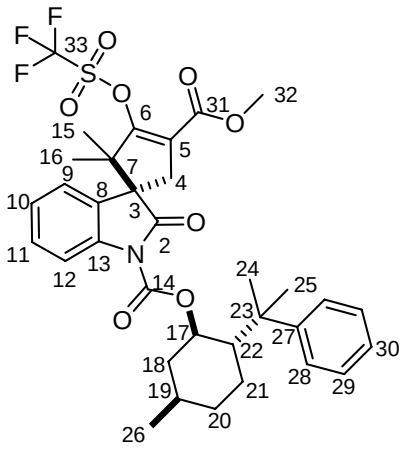
4.79

Ketoester 4.79 (mp5-081). A solution of *n*-BuLi (1.22 mL, 2.23 M, 2.73 mmol) in hexanes was added to a solution of *i*-Pr_2NH (0.42 mL, 3.00 mmol) in THF (3.8 mL) at

−78 °C. The solution was stirred at −78 °C for 15 min, whereupon the dry ice/acetone bath was replaced with an ice bath, and the reaction was stirred at 0 °C for 15 min. The LDA solution was added dropwise via cannula to a stirred solution of **4.77** (605 mg, 1.24 mmol) in THF (12.4 mL) at −78 °C, and the reaction mixture was stirred for 20 min. CH_3OCOCN (0.39 mL, 4.96 mmol) was added, the reaction was stirred at −78 °C for 1 h and at −40 °C for 1 h, and saturated aqueous 0.5 M HCl (5 mL) was added. The cold bath was removed, and the reaction mixture was allowed to warm to room temperature and poured in 0.5 M HCl (100 mL). The mixture was extracted with EtOAc (3 × 100 mL), and the combined organic phases were dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with hexanes / EtOAc (4:1) to give 542 mg (80%) of **4.79** as a foam; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86-7.76 (m, 1 H), 7.38-7.34 (m, 1 H), 7.29-7.27 (m, 1 H), 7.23 (dd, *J* = 8.5, 1.1 Hz, 2 H), 7.20 (td, *J* = 7.5, 1.1 Hz, 1 H), 7.03-7.00 (comp, 2 H), 6.86-82 (m, 1 H), 5.08 (td, *J* = 10.8, 4.6 Hz, 1 H), 3.99 (dd, *J* = 10.7, 9.3 Hz, 1 H), 3.80 (s, 3 H), 2.77 (dd, *J* = 13.8, 10.7 Hz, 1 H), 2.39 (dd, *J* = 13.8, 9.3 Hz, 1 H), 2.17 (ddd, *J* = 12.2, 10.8, 3.5 Hz, 1 H), 1.95-1.90 (m, 1 H), 1.79-1.74 (m, 1 H), 1.66-1.62 (m, 1 H), 1.52-1.42 (m, 1 H), 1.34 (s, 3H), 1.24 (s, 3 H), 1.26-1.10 (comp, 2 H), 1.15 (s, 3H), 0.88 (d, *J* = 6.6 Hz, 3 H), 0.80 (s, 3 H); ^{13}C NMR (125 MHz) δ 210.1, 177.2, 169.9, 151.1, 149.7, 140.2, 129.0, 127.8, 125.9, 125.4, 124.9, 124.8, 124.3, 115.2, 77.6, 56.6, 53.7, 52.9, 50.9, 50.5, 41.7, 39.7, 34.2, 31.9, 31.4, 28.1, 26.5, 24.7, 21.7, 20.9, 18.0; IR (neat) 2955, 1760, 1727, 1464, 1284, 1245, 1160 cm^{-1}; mass spectrum (CI) *m/z* 546.2855 [$C_{33}H_{40}NO_6$ (M+1) requires 546.2856], 530, 546 (base), 574.

NMR Assignments. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86-7.76 (m, 1 H, C9-H or C12-H), 7.38-7.34 (m, 1 H, C10-H or C11-H), 7.29-7.27 (m, 1 H, C9-H or C12-H), 7.23 (dd, *J* = 8.5, 1.1 Hz, 2 H, C28-H), 7.20 (td, *J* = 7.5, 1.1 Hz, 1 H, C10-H or C11-H), 7.03-

7.00 (comp, 2 H, C29-H), 6.86-82 (m, 1 H, C30-H), 5.08 (td, *J* = 10.8, 4.6 Hz, 1 H, C17-H), 3.99 (dd, *J* = 10.7, 9.3 Hz, 1 H, C5-H), 3.80 (s, 3 H, C32-H), 2.77 (dd, *J* = 13.8, 10.7 Hz, 1 H, C4-H), 2.39 (dd, *J* = 13.8, 9.3 Hz, 1 H, C4-H), 2.17 (ddd, *J* = 12.2, 10.8, 3.5 Hz, 1 H, C22-H), 1.95-1.90 (m, 1 H, C18-H), 1.79-1.74 (m, 1 H, C21-H), 1.66-1.62 (m, 1 H, C20-H), 1.52-1.42 (m, 1 H, C19-H), 1.34 (s, 3H, C24-H or C25-H), 1.24 (s, 3 H, C15-H or C-16), 1.26-1.10 (comp, 2 H, C18-H, C21-H), 1.15 (s, 3H, C24-H or C25-H), 0.88 (d, *J* = 6.6 Hz, 3 H, C26-H), 0.80 (s, 3 H, C15-H or C16-H); ^{13}C NMR (125 MHz) δ 210.1 (C6), 177.2 (C2), 169.9 (C31), 151.1 (C14), 149.7 (C27), 140.2 (C13), 129.0 (C10 or C11), 127.8 (C29), 125.9 (C8), 125.4 (C28), 124.9 (C9 or C12), 124.8 (C30), 124.3 (C10 or C11), 115.2 (C9 or C12), 77.6 (C17), 56.6 (C3), 53.7 (C7), 52.9 (C32), 50.9 (C22), 50.5 (C5), 41.7 (C18), 39.7 (C23), 34.2 (C20), 31.9 (C4), 31.4 (C19), 28.1 (C15 or C16), 26.5 (C21), 24.7 (C24 or C25), 21.7 (C26), 20.9 (C24 or C25), 18.0 (C15 or C16).



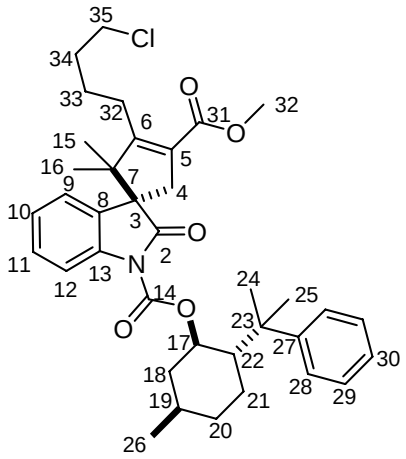
4.80

Triflate 4.80 (mp5-082). A solution of potassium hexamethyldisilazide (4.0 mL, 0.5 M, 1.98 mmol) in toluene was added to a stirred solution of **4.79** (542 mg, 0.99 mmol) in toluene (10 mL) at –78 ˚C. The reaction was stirred for 20 min, whereupon Tf_2O (0.67 mL, 3.96 mmol) was added. The cold bath removed, and the reaction was

stirred 2 h, whereupon it was poured into a separatory funnel containing saturated aqueous $NaHCO_3$ (75 mL). The mixture was extracted with EtOAc (3 x 70 mL), and the combined organic layers were dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with hexanes / EtOAc (4:1) to give 509 mg (76%) of **4.80** as a tan oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.8 Hz, 1 H), 7.34-7.30 (m, 1 H), 7.29-7.27 (m, 1 H), 7.24-7.22 (comp, 2 H), 7.14 (td, *J* = 7.6, 1.0 Hz, 1 H), 7.00-6.96 (comp, 2 H), 6.85-6.81 (m, 1 H), 5.10 (td, *J* = 10.7, 4.6 Hz, 1 H), 3.84 (s, 3 H), 3.13 (d, *J* = 16.3 Hz, 1 H), 2.90 (d, *J* = 16.3 Hz, 1 H), 2.18 (ddd, *J* = 12.2, 10.7, 3.6 Hz, 1 H), 1.96-1.91 (m, 1 H), 1.78 (dq, *J* = 13.4, 3.6 Hz, 1 H), 1.68-1.63 (m, 1 H), 1.52-1.44 (m, 1 H), 1.35 (s, 3H), 1.24 (s, 3 H), 1.17-1.11 (comp, 1 H), 1.14 (s, 3H), 0.96-0.90 (m, 1 H), 0.93 (s, 3 H), 0.87 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz) δ 173.8, 162.2, 155.9, 151.0, 149,7, 139.2, 129.9, 128.0, 127.8, 125.4, 124.9, 124.4, 123.9, 119.4, 115.1, 77.4, 56.4, 52.1, 52.0, 50.6, 41.7, 39.7, 37.1, 34.2, 31.5, 28.3, 26.5, 24.6, 21.8, 21.7, 21.2; IR (neat) 2957, 1769, 1727, 1428, 1241, 1214, 1138, 1088, 845, 765 cm^{-1}; mass spectrum (CI) *m/z* 678.2345 [$C_{34}H_{39}F_3NO_8$ S(M+1) requires 678.2348], 388,420, 678 (base).

NMR Assignments. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.8 Hz, 1 H, C9-H or C12-H), 7.34-7.30 (m, 1 H, C10-H or C11-H), 7.29-7.27 (m, 1 H, C9-H or C12-H), 7.24-7.22 (comp, 2 H, C28-H), 7.14 (td, *J* = 7.6, 1.0 Hz, 1 H, C10-H or C11-H), 7.00-6.96 (comp, 2 H, C29-H), 6.85-6.81 (m, 1 H, C30-H), 5.10 (td, *J* = 10.7, 4.6 Hz, 1 H, C17-H), 3.84 (s, 3 H, C32-H), 3.13 (d, *J* = 16.3 Hz, 1 H, C4-H), 2.90 (d, *J* = 16.3 Hz, 1 H, C4-H), 2.18 (ddd, *J* = 12.2, 10.7, 3.6 Hz, 1 H, C22-H), 1.96-1.91 (m, 1 H, C18-H), 1.78 (dq, *J* = 13.4, 3.6 Hz, 1 H, C21-H), 1.68-1.63 (m, 1 H, C20-H), 1.52-1.44 (m, 1 H, C19-H), 1.35 (s, 3H, C24-H or C25-H), 1.24 (s, 3 H, C15-H or C-16), 1.17-1.11 (comp, 1 H, C21-H), 1.14 (s, 3H, C24-H or C25-H), 0.96-0.90 (m, 1 H, C20-H), 0.93 (s, 3 H,

C15-H or C16-H), 0.87 (d, J = 6.6 Hz, 3 H, C26-H); ^{13}C NMR (125 MHz) δ 173.8 (C2), 162.2 (C31), 155.9 (C6), 151.0 (C14), 149,7 (C27), 139.2 (C13), 129.9 (C10 or C11), 128.0 (C8), 127.8 (C29), 125.4 (C28), 124.9 (C30), 124.4 (C10 or C11), 123.9 (C9 or C10), 119.4 (C5), 115.1 (C9 or C12), 77.4 (C17), 56.4 (C3), 52.1 (C7), 52.0 (C32), 50.6 (C22), 41.7 (C18), 39.7 (C23), 37.1 (C4), 34.2 (C20), 31.5 (C19), 28.3 (C15 or C16), 26.5 (C21), 24.6 (C24 or C25), 21.8 (C26), 21.7 (C15 or C16), 21.2 (C24 or C25).



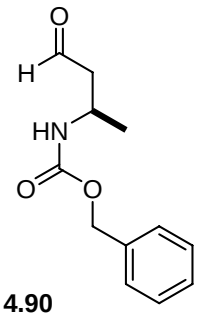
4.84

Enoate 4.84 (mp4-023). Dibromoethane (13 mg, 6 μL, 0.07 mmol) was added to a suspension of zinc (124 mg, 1.89 mmol) in THF (0.2 mL), and the resulting mixture was heated to 65 ˚C for 1 min. The mixture was allowed to cool to room temperature, and TMSCl (6 mg, 7 μg, 0.06 mmol) was added. The mixture was stirred for 15 min, whereupon a solution of 4-chloro-1-iodobutane (393 mg, 0.22 mL, 1.80 mmol) in THF (1 mL) was added, and the reaction was stirred over night at 35 ˚C. The opaque supernate was transferred via cannula to a separate flask leaving unreacted zinc behind, and the solids were washed with THF (2 x 0.5 mL). The solution was cooled to –78 ˚C, and a solution of MeLi (1.10 mL, 1.56 M, 1.72 mmol) was added followed by a solution of CuCN (95 mg, 1.06 mmol) and LiCl (89 mg, 2.11 mmol) in THF (2.1 mL). The mixture

was stirred at –78 ˚C for 10 min, whereupon a solution of **4.80** (41 mg, 0.06 mmol) in THF (1.5 mL) was added. The cold bath was removed, and the reaction was stirred 1 h, whereupon a mixture of saturated aqueous NH_4Cl/NH_4OH (9:1, 5 mL) was added, and resulting slurry was stirred for 30 min. The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with hexanes / EtOAc (2:1) to provide 29 mg (77%) of **4.84** as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70-7.68 (m, Hz, 1 H), 7.28-7.26 (m, 1 H), 7.25-7.23 (comp, 2 H), 7.19 (dd, *J* = 7.6, 1.8 Hz, 1 H), 7.08 (td, *J* = 7.4, 1.0 Hz, 1 H), 7.01 (t, *J* = 7.4, 1.0 Hz 2 H), 6.87-6.84 (m, 1 H), 5.10 (td, *J* = 10.8, 4.6 Hz, 1 H), 3.75 (s, 3 H), 3.57 (td, *J* = 6.6, 1.2 Hz, 1 H), 3.08 (d, *J* = 16.3 Hz, 1 H), 2.80 (d, *J* = 16.3 Hz, 1 H), 2.48-2.37 (comp, 2 H), 2.17 (ddd, *J* = 14.3, 10.6, 3.6 Hz, 1 H), 1.99-1.94 (m, 1 H), 1.96-1.85 (comp, 2 H), 1.74-1.60 (comp, 4 H), 1.51-1.43 (m, 1 H), 1.35 (s, 3H), 1.25 (s, 3 H), 1.28-1.22 (m, 1 H), 1.18-1.09 (m, 1 H), 1.03 (s, 3H), 0.88 (d, *J* = 6.4 Hz, 3 H), 0.84 (s, 3H); ^{13}C NMR (125 MHz) δ 175.2, 165.5, 163.6, 150.9, 149.9, 139.1, 130.0, 128.2, 127.8, 125.4, 125.0, 124.9, 123.9, 123.7, 114.8, 72.9, 58.7, 56.2, 51.3, 50.6, 44.6, 41.8, 40.6, 39.8, 34.3, 33.1, 31.5, 27.7, 26.6, 26.5, 26.4, 25.3, 23.2, 22.2, 21.7; IR (neat) 2956, 1767, 1716, 1358, 1293, 1250 cm^{-1}; mass spectrum (CI) *m/z* 619.3069 [$C_{37}H_{46}NO_5Cl$(M+) requires 619.3069], 585, 620, 621 (base), 623, 624.

NMR Assignments. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70-7.68 (m, Hz, 1 H, C9-H or C12-H), 7.28-7.26 (m, 1 H, C10-H or C11-H), 7.25-7.23 (comp, 2 H, C28-H), 7.19 (dd, *J* = 7.6, 1.8 Hz, 1 H, C9-H or C12-H), 7.08 (td, *J* = 7.4, 1.0 Hz, 1 H, C10-H or C11-H), 7.01 (t, *J* = 7.4, 1.0 Hz 2 H, C29-H), 6.87-6.84 (m, 1 H, C30-H), 5.10 (td, *J* = 10.8, 4.6 Hz, 1 H, C17-H), 3.75 (s, 3 H, C32-H), 3.57 (td, *J* = 6.6, 1.2 Hz, 1 H, C33-H), 3.08 (d, *J* = 16.3 Hz, 1 H, C4-H), 2.80 (d, *J* = 16.3 Hz, 1 H, C4-H), 2.48-2.37 (comp, 2 H,

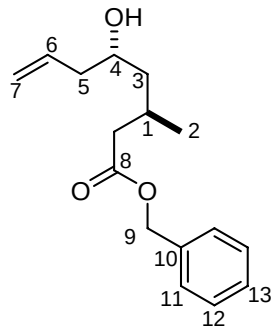
C36-H), 2.17 (ddd, J = 14.3, 10.6, 3.6 Hz, 1 H, C22-H), 1.99-1.94 (m, 1 H, C18-H), 1.96-1.85 (comp, 2 H, C34-H), 1.74-1.60 (comp, 4 H, C20-H, C21-H, C35-H), 1.51-1.43 (m, 1 H, C19-H), 1.35 (s, 3H, C24-H or C25-H), 1.25 (s, 3 H, C15-H or C-16), 1.28-1.22 (m, 1 H, C18-H), 1.18-1.09 (m, 1 H, C21-H), 1.03 (s, 3H, C15-H or C16-H), 0.88 (d, J = 6.4 Hz, 3 H, C26-H), 0.84 (s, 3H, C15-H or C16-H); ^{13}C NMR (125 MHz) δ 175.2 (C2), 165.5 (C31), 163.6 (C6), 150.9 (C14), 149.9 (C27), 139.1 (C13), 130.0 (C5), 128.2 (C10 or C11), 127.8 (C29), 125.4 (C28), 125.0 (C30), 124.9 (C8), 123.9 (C10 or C11), 123.7 (C9 or C12), 114.8 (C9 or C12), 72.9 (C17), 58.7 (C3), 56.2 (C7), 51.3 (C32), 50.6 (C22), 44.6 (C33), 41.8 (C18), 40.6 (C4), 39.8, (C23), 34.3 (C20), 33.1 (C34), 31.5 (C19), 27.7 (C15 or C16), 26.6 (C21 or C35 or C36), 26.5 (C21 or C35 or C36), 26.4 (C21 or C35 or C36), 25.3 (C24 or C25), 23.2 (C15 or C16), 22.2 (C24 or C25), 21.7 (C26).



4.90

(1-Methyl-3-oxopropyl)carbamic acid benzyl ester (4.90) (mp3-224, mp3-225, mp3-226). A solution of SO_3·Py (9.0 g, 57.0 mmol) in DMSO (60 mL) was added to a solution of **4.88** (4.0 g, 19.1 mmol) and Et_3N (7.9 mL, 57.0 mmol) in CH_2Cl_2 (60 mL) at –10 °C. The cold bath was removed and the reaction was stirred for 15 min, whereupon it was poured into brine (200 mL) and crushed ice (200 mL). The aqueous mixture was extracted with Et_2O (3 x 200 mL), and the combined organic layers were washed with 10% citric acid (100 mL) and brine (100 mL). The organic layer was dried (Na_2SO_4) and

concentrated under reduced pressure to give the crude **4.89**, which was used in the next step without further purification. In a separate flask NaHMDS (13.4 mL, 2.0 M, 26.7 mmol) was added to a slurry of (methoxymethyl)triphenylphosphonium bromide (9.15 g, 26.7 mmol) in THF (60 mL) at −78 °C. The cold bath was replaced with a 0 °C ice bath, and the reaction was stirred at this temperature for 40 min. The reaction was cooled to −78 °C, and a solution of the crude **4.89** in THF (40 mL) was added drop wise. The cold bath was replaced with a 0 °C ice bath, and the reaction was stirred at this temperature for 40 min and then at room temperature for 30 min. The reaction was diluted in Et_2O (200 mL) and filtered through celite. The solids were washed with Et_2O (100 mL), and the combined washings and filtrate were washed with 1 M HCl (3 x 100 mL) and a 50% saturated aqueous solution of $NaHCO_3$ (100 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was filtered through a pug of silica eluting with Et_2O, and the volatiles were removed under reduced pressure. The residue was dissolved in acetone (50 mL), and $TsOH{\cdot}H_2O$ (1.82 g, 9.55 mmol) was added. The reaction was stirred at room temperature over night, whereupon the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (200 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (100 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to 1.82 g (43%) of **4.90** as a clear colorless oil. The ^1H NMR spectrum was identical to that reported in the literature.[173]

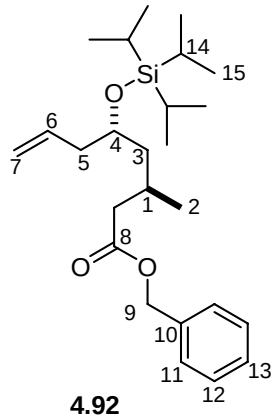


4.91

***N*-(3-Hydoxy-1-methyl-hex-5-enyl)-3-phenylpropionamide (4.91) (mp3-092).** A solution of allylmagnesium bromide (0.35 mL, 1.0 M, 0.35 mmol) was added to a solution of (-)-DIP-Cl (134 mg, 0.42 mmol) in Et_2O (2 mL) cooled to –78 ˚C. The reaction was stirred at –78 ˚C for 5 min, whereupon the cold bath was replaced with and ice water bath and the mixture was stirred for 1 h. The reaction was cooled to –78 ˚C, whereupon a solution of aldehyde **4.90** (70 mg, 0.32 mmol) in Et_2O (0.7 mL + 0.3 mL rinse) was added via canula. Stirring was continued for 1 h, whereupon phosphate buffer (2 mL) and MeOH (2 mL) were added and the cold bath was removed. After stirring for 30 min, the reaction was poured into a separatory funnel containing saturated aqueous $NaHCO_3$ (10 mL), and extracted with ether (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with hexanes/EtOAc (2:1 → 1:1) to 55 mg (66%) of **4.91** as a clear colorless oil; ^{1}NMR (500 MHz) δ 7.34-7.27 (comp, 5 H), 5.82-5.73 (m, 1 H), 5.12-5.04 (comp, 4 H), 4.98 (br s, 1 H), 3.87-3.80 (m, 1 H), 3.74-3.69 (m, 1 H), 2.31-2.22 (m, H), 2.18-2.11 (m, H), 1.63-1.52 (comp, 2 H), 1.17 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz) δ 156.0, 136.6, 134.4, 128.5, 128.0, 118.3, 68.8, 66.5, 45.7, 43.7, 42.3, 21.6; IR (neat) 3325, 3069, 2973, 2932, 1694, 1537, 1257, 1088, 915, 697 cm-

[1]; mass spectrum (CI) *m/z* 264.1597 [$C_{15}H_{22}NO_3$ (M+1) requires 264.1600], 220, 246, 264 (base), 354.

NMR Assignments. [1]NMR (500 MHz) δ 7.34-7.27 (comp, 5 H, C11-H, C12-H, C13-H), 5.82-5.73 (m, 1 H, C6-H), 5.12-5.04 (comp, 4 H, C7-H, C9-H), 4.98 (br s, 1 H, NH), 3.87-3.80 (m, 1 H, C1-H), 3.74-3.69 (m, 1 H, C4-H), 2.31-2.22 (m, H, C5-H), 2.18-2.11 (m, H, C5-H), 1.63-1.52 (comp, 2 H, C3-H), 1.17 (d, *J* = 6.6 Hz, 3 H, C2-H); [13]C NMR (125 MHz) δ 156.0 (C8), 136.6 (C10), 134.4 (C6), 128.5 (Ar-C), 128.0 (Ar-C), 118.3 (C7), 68.8 (C4), 66.5 (C9), 45.7 (C1), 43.7 (C3), 42.3 (C5), 21.6 (C2).

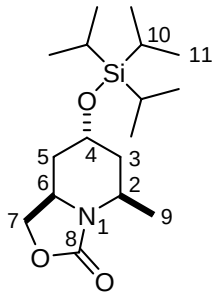


4.92

***N*-(1-methyl-3-triisopropylsilanyloxy-hex-5-enyl)-3-phenylpropionamide (4.92) (mp3-106).** 2,6-lutidine (83 mg, 90 μL, 0.76 mmol) followed by TIPSOTf (171 mg, 0.15 mL, 0.57 mmol) were added to a solution of **4.91** (100 mg, 0.38 mmol) in CH_2Cl_2 (3.8 mL) cooled to 0 ˚C. The reaction was stirred at 0 ˚C for 40 min, whereupon MeOH (0.5 mL) was added and the reaction. Stirring was continued for 5 min, whereupon the reaction mixture was poured into a separatory funnel containing 0.5 M HCl (15 mL), and extracted with ether (3 x 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with 10% Et_2O/pentane to give 159 mg (99%) of **4.92** as a

white solid: mp = 45-47 ˚C; ^{1}NMR (500 MHz) δ 7.35-7.27 (comp, 5 H), 5.85-5.79 (m, 1 H), 5.07-5.03 (comp, 4 H), 4.66 (d, *J* = 6.8 Hz, 1 H), 3.95-3.92 (m, 1 H), 3.83-3.77 (m, 1 H), 2.58-2.30 (comp, 2 H), 1.68-1.52 (comp, 2 H), 1.15 (d, *J* = 6.4 Hz, 3 H), 1.05-0.97 (m, 3 H) 1.03 (s, 18 H); ^{13}C NMR (125 MHz) δ 155.6, 136.7, 134.4, 128.5, 128.1, 128.0, 117.4, 69.8, 66.4, 44.8, 43.8, 41.3, 22.2, 18.15, 18.13, 12.6; IR (neat) 3315, 2942, 2866, 1696, 1536, 1462, 1254, 1088, 1056 cm^{-1}; mass spectrum (CI) *m/z* 420.2932 [$C_{24}H_{42}NO_3Si$ (M+1) requires 420. 2934], 246, 376 (base), 420.

NMR Assignments. ^{1}NMR (500 MHz) δ 7.35-7.27 (comp, 5 H, C11-H, C12-H, C13-H), 5.85-5.79 (m, 1 H, C6-H), 5.07-5.03 (comp, 4 H, C7-H, C9-H), 4.66 (d, *J* = 6.8 Hz, 1 H, NH), 3.95-3.92 (m, 1 H, C4-H), 3.83-3.77 (m, 1 H, C1-H), 2.58-2.30 (comp, 2 H, C5-H), 1.68-1.52 (comp, 2 H, C3-H), 1.15 (d, *J* = 6.4 Hz, 3 H, C2-H), 1.05-0.97 (m, 3 H, C15-H) 1.03 (s, 18 H, C14-H); ^{13}C NMR (125 MHz) δ 155.6 (C8), 136.7 (C10), 134.4 (C6), 128.5 (Ar-C), 128.1 (Ar-C), 128.0 (Ar-C), 117.4 (C7), 69.8 (C4), 66.4 (C9), 44.8 (C1), 43.8 (C3), 41.3 (C5), 22.2 (C2), 18.15 (C14), 18.13 (C14), 12.6 (C15).

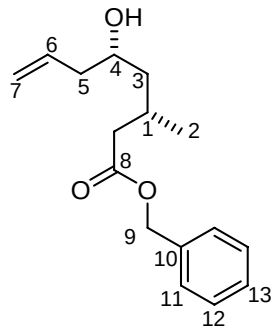


4.95

5-Methyl-7-triisopropylsilanyloxyhexahydrooxazolo[3,4-*a*]pyridine-3-one (4.95) (mp3-202, mp3-213). $Hg(OAc)_2$ (57 mg, 0.18 mmol) was added to a solution of **4.92** (30 mg, 0.07 mmol) in THF (2.1 mL) and the reaction was stirred at room temperature for 2 days. A saturated aqueous solution of KBr was added and the mixture

was stirred for 1.5 h, whereupon it was poured into H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 20% Et_2O/pentane to give 35 mg (70%) of **4.94**, which was dissolved in CH_2Cl_2 (1 mL). Iodine (19 mg, 0.15 mmol) was added and the reaction was heated to 45 °C for 2 h, whereupon the reaction was allowed to cool to room temperature. A saturated aqueous solution of $Na_2S_2O_3$ (0.5 mL) was added, and the slurry was poured into H_2O (4 mL) and extracted with CH_2Cl_2 (2 x 4 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexanes (1:3) to give 10 mg (61%) of **4.95**, as a white solid: ^{1}NMR (400 MHz) δ 4.31 (t, *J* = 7.9 Hz, 1 H), 4.31-4.27 (m, 1 H), 4.03 (dtd, *J* = 11.3, 7.9, 3.1 Hz, 1 H), 3.75 (t, *J* = 7.9 Hz, 1 H), 3.72-3.63 (m, 1 H), 1.88-1.82 (m, 1 H), 1.74-1.72 (m, 1 H), 1.56 (d, *J* = 6.5 Hz, 3 H), 1.52-1.43 (comp, 2 H), 1.11-0.99 (comp, 21 H).

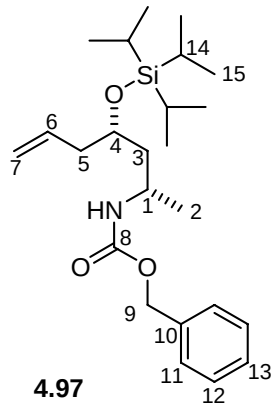
NMR Assignments. ^{1}NMR (400 MHz) δ 4.31 (t, *J* = 7.9 Hz, 1 H, C7-H), 4.31-4.27 (m, 1 H, C4-H), 4.03 (dtd, *J* = 11.3, 7.9, 3.1 Hz, 1 H, C6-H), 3.75 (t, *J* = 7.9 Hz, 1 H, C7-H), 3.72-3.63 (m, 1 H, C2-H), 1.88-1.82 (m, 1 H, C3-H or C5-H), 1.74-1.72 (m, 1 H, C3-H or C5-H), 1.56 (d, *J* = 6.5 Hz, 3 H, C9-H), 1.52-1.43 (comp, 2 H, C3-H or C5-H), 1.11-0.99 (comp, 21 H, C10-H, C11-H).



***N*-(3-Hydoxy-1-methyl-hex-5-enyl)-3-phenylpropionamide (mp3-227).** A solution of allylmagnesium bromide (9.1 mL, 1.0 M, 9.1 mmol) was added to a stirred solution of (-)-DIP-Cl (3.50 g, 10.9 mmol) in Et_2O (50 mL) at –78 ˚C. The reaction was stirred at –78 ˚C for 5 min, whereupon the cold bath was replaced with an ice water bath, and the mixture was stirred for 1 h. The reaction was cooled to –78 ˚C, whereupon a solution of aldehyde **4.90** (1.82 g, 8.23 mmol) in Et_2O (20 mL + 5 mL rinse) was added via canula. Stirring was and for 1 h, whereupon phosphate buffer (40 mL), MeOH (40 mL), and a 30% aqueous solution of H_2O_2 (20 mL) were added. The cold bath was removed, and stirring was continued for 30 min. The reaction was poured into a separatory funnel containing saturated aqueous $NaHCO_3$ (100 mL), and the mixture was extracted with Et_2O (3 x 100 mL). The combined organic extracts were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (2:1) to 1.46 g (67%) of the title compound as a clear colorless oil; ^{1}NMR (500 MHz) δ 7.40-7.32 (comp, 5 H), 5.90-5.81 (m, 1 H), 5.14-5.09 (comp, 4 H), 4.82 (br d, *J* =7.4 Hz, 1 H), 4.08-3.98 (m, 1 H), 3.76-3.68 (m, 1 H), 2.31-2.18 (comp, 2 H), 1.58 (ddd, *J* = 14.1, 10.6, 3.2 Hz, 1 H), 1.42 (ddd, *J* = 14.1, 10.4, 2.2 Hz, 1 H), 1.22 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz) δ 157.0, 136.4, 135.1, 128.5, 128.2, 128.1, 117.3, 67.2, 66.9, 44.9, 44.1, 41.6, 21.4; IR (neat) 3322, 2972, 2932,

1537, 1693, 1255, 1043 cm^{-1}; mass spectrum (CI) *m/z* 264.1600 [$C_{15}H_{22}NO_3$ (M+1) requires 264.1600], 220, 246, 264 (base).

NMR Assignments. ^{1}NMR (500 MHz) δ 7.40-7.32 (comp, 5 H, C12-H, C13-H, C14-H), 5.90-5.81 (m, 1 H, C7-H), 5.14-5.09 (comp, 4 H, C8-H, C10-H), 4.82 (br d, *J* =7.4 Hz, 1 H, NH), 4.08-3.98 (m, 1 H, C2-H), 3.76-3.68 (m, 1 H, C5-H), 2.31-2.18 (comp, 2 H, C6-H), 1.58 (ddd, *J* = 14.1, 10.6, 3.2 Hz, 1 H, C4-H), 1.42 (ddd, *J* = 14.1, 10.4, 2.2 Hz, 1 H, C4-H), 1.22 (d, *J* = 6.6 Hz, 3 H, C3-H); ^{13}C NMR (125 MHz) δ 157.0 (C9), 136.4 (C11), 135.1 (C7), 128.5 (Ar-C), 128.2 (Ar-C), 128.1 (Ar-C), 117.3 (C8), 67.2 (C5), 66.9 (C10), 44.9 (C4), 44.1 (C2), 41.6 (C6), 21.4 (C3).

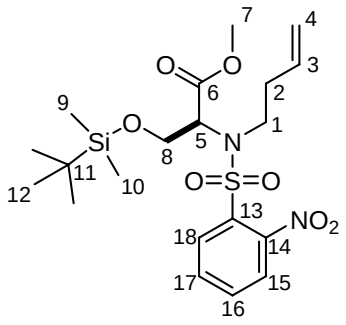


4.97

***N*-(1-Methyl-3-triisopropylsilanyloxy-hex-5-enyl)-3-phenylpropionamide (4.97) (mp3-228).** 2,6-Lutidine (1.19 g, 1.29 mL, 11.1 mmol) and TIPSOTf (2.55 g, 2.23 mL, 8.31 mmol) were added to a stirred solution of *N*-(3-hydoxy-1-methyl-hex-5-enyl)-3-phenylpropionamide (1.46 g, 5.54 mmol) in CH_2Cl_2 (50 mL) at 0 ˚C. The reaction was stirred at 0 ˚C for 1.5 h, whereupon MeOH (2 mL) was added. Stirring was continued for 5 min, whereupon the reaction mixture was poured into a separatory funnel containing 0.5 M HCl (50 mL). The mixture was extracted with ether (3 x 50 mL), and the combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated

under reduced pressure. The residue was purified by flash chromatography eluting with 10% → 20% Et_2O in pentane in water give 1.50 g (66%) of **4.97** as colorless oil; ^{1}NMR (500 MHz) δ 7.33-7.25 (comp, 5 H), 5.73 (ddt, *J* = 17.3, 10.2, 7.1 Hz, 1 H), 5.32, (br s, 1 H), 5.08-5.02 (comp, 4 H), 4.01-3.96 (m, 1 H), 3.86-3.80 (m, 1 H), 2.34-2.29 (comp, 2 H), 1.68-1.54 (comp, 2 H), 1.17 (d, *J* = 5.5 Hz, 3 H), 1.07-1.0 (comp, 21 H); ^{13}C NMR (125 MHz) δ 155.8, 136.8, 134.2, 128.4, 127.92, 127.88, 117.6, 70.2, 66.3, 44.5, 42.2, 41.3, 21.8, 18.2, 18.1, 12.6, 12.3; IR (neat) 3338, 2942, 2866 1701, 1463, 1259, 1060, 883 cm^{-1} mass spectrum (CI) *m/z* 420.2932 [$C_{24}H_{42}NO_3Si$ (M+1) requires 420. 2934], 246, 376 (base), 420.

NMR Assignments. ^{1}NMR (500 MHz) δ 7.33-7.25 (comp, 5 H, C12-H, C13-H, C14-H), 5.73 (ddt, *J* = 17.3, 10.2, 7.1 Hz, 1 H, C7-H), 5.32, (br s, 1 H, NH), 5.08-5.02 (comp, 4 H, C8-H, C10-H), 4.01-3.96 (m, 1 H, C5-H), 3.86-3.80 (m, 1 H, C2-H), 2.34-2.29 (comp, 2 H, C6-H), 1.68-1.54 (comp, 2 H, C4-H), 1.17 (d, *J* = 5.5 Hz, 3 H, C3-H), 1.07-1.0 (comp, 21 H, C15-H, C16-H); ^{13}C NMR (125 MHz) δ 155.8 (C9), 136.8 (C11), 134.2 (C7), 128.4 (Ar-C), 127.92 (Ar-C), 127.88 (Ar-C), 117.6 (C8), 70.2 (C5), 66.3 (C10), 44.5 (C2), 42.2 (C4), 41.3 (C6), 21.8 (C3), 18.2 (C16), 18.1 (C16), 12.6 (C15), 12.3 (C15).

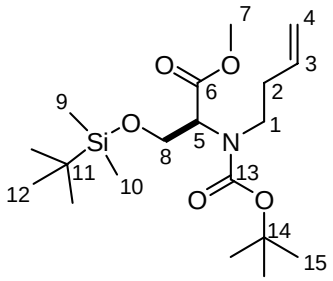


4.105

2-[But-3-enyl-(2-nitro-benzenesulfonyl)amino]-3-(tert-butyldimethyl-silanyloxy)-propionic acid methyl ester (4.105), (mp4-035, mp4-036, mp4-039). A solution of **4.103** (2.00 g, 12.9 mmol), TBSCl (2.90 g, 19.4 mmol) and imidazole (3.10 g, 45.2 mmol) in CH_2Cl_2 (64 mL) was stirred at room temperature for 4 h, whereupon it was poured into EtOAc (300 mL). The mixture was washed with 0.5 M HCl (2 x 100 mL), and the organic layer was dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (60 mL). Et_3N (6.3 mL, 45.2 mmol) and NsCl (4.30 g, 19.4 mmol) were added, and the reaction was stirred at room temperature for 1 h, whereupon it was poured into EtOAc (300 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (100 mL), 1 M $KHSO_4$ (2 x 50 mL), 0.5 M HCl (100 mL) and brine (100 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc / hexanes (1:1) to give 5.2 g (96%) of **4.104** as a yellow oil. DEAD (3.00 mL, 19.1 mmol) was added dropwise over 10 min to a solution of **4.104** (4.00 g, 9.56 mmol) and PPh_3 (6.00 g, 22.9 mmol) in THF (50 mL) at 0 °C. The ice bath was removed, and the reaction was stirred overnight. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc / hexanes (1:2) to give 3.7 g (82%) of **4.105** as a yellow oil. ^{1}NMR (400 MHz) δ 8.08-8.05 (m, 1 H), 7.68-7.63 (comp, 2 H), 7.58-7.54 (m, 1 H), 5.75-5.64 (m, 1 H), 5.06-4.98 (comp, 2 H), 4.77 (dd, *J* = 5.5, 2.7 Hz, 1 H), 4.22 (dd, *J* = 11.0, 5.5 Hz, 1 H), 4.04 (dd, *J* = 11.0, 2.7 Hz, 1 H), 3.60 (s, 3 H), 3.58-3.41 (comp, 2 H), 0.83 (s, 9), 0.04 (s, 3 H), 0.03 (s, 3 H).

NMR Assignments. ^{1}NMR (400 MHz) δ 8.08-8.05 (m, 1 H, C15-H), 7.68-7.63 (comp, 2 H, C16-H, C17-H), 7.58-7.54 (m, 1 H, C18-H), 5.75-5.64 (m, 1 H, C3-H), 5.06-4.98 (comp, 2 H, C4-H), 4.77 (dd, *J* = 5.5, 2.7 Hz, 1 H, C5-H), 4.22 (dd, *J* = 11.0, 5.5 Hz, 1 H, C8-H), 4.04 (dd, *J* = 11.0, 2.7 Hz, 1 H, C8-H), 3.60 (s, 3 H, C7-H), 3.58-3.41 (comp,

2 H, C2-H), 0.83 (s, 9 H, C12-H), 0.04 (s, 3 H, C9-H or C10-H), 0.03 (s, 3 H, C9-H or C10-H).

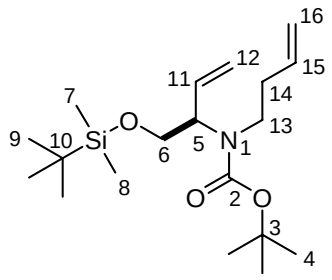


4.106

2-[But-3-enyl-*tert*-butoxycarbonylamino]-3-(tert-butyldimethyl-silanyloxy)-propionic acid methyl ester (4.106), (mp4-040, mp4-041). K_2CO_3 (3.16 g, 22.9 mmol) was added to a solution of **4.105** (3.6 g, 6.62 mmol) and thiophenol (0.95 mL, 9.14 mmol) in DMF (20 mL) at 0 °C. The reaction was stirred at 0 °C for 1 h, whereupon it was poured into Et_2O (150 mL) and washed with brine (75 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was dissolved in THF (40 mL) and Boc_2O (2.4 mL) and DMAP (93 mg, 0.76 mmol) were added. The reaction was stirred at room temperature overnight, whereupon it was concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc / hexanes (1:8) to give 1.3 g (52%) of **4.106** as a pale yellow oil; ^{1}NMR (500 MHz) δ 5.78-5.72 (m, 1 H), 5.09-5.00 (comp, 2 H), 4.40 (dd, *J* = 7.5, 3.8 Hz, 0.6 H), 4.34 (dd, *J* = 7.5, 4.1 Hz, 0.4 H), 4.17-4.04 (comp, 2 H), 3.64-3.48 (m, 1 H), 3.71 (s, 3 H), 3.37-3.29 (m, 1 H), 2.45-2.35 (comp, 2 H), 1.51 (s, 5.4 H), 1.49 (s, 3.6 H), 0.86 (s, 3.6 H), 0.85 (s, 5.4 H), 0.05-0.03 (comp, 3 H).

NMR Assignments. ^{1}NMR (500 MHz) δ 5.78-5.72 (m, 1 H, C3-H), 5.09-5.00 (comp, 2 H, C4-H), 4.40 (dd, *J* = 7.5, 3.8 Hz, 0.6 H, C5-H), 4.34 (dd, *J* = 7.5, 4.1 Hz, 0.4

H, C5-H), 4.17-4.04 (comp, 2 H, C8-H), 3.64-3.48 (m, 1 H, C1-H), 3.71 (s, 3 H, C7-H), 3.37-3.29 (m, 1 H, C1-H), 2.45-2.35 (comp, 2 H, C2-H), 1.51 (s, 5.4 H, C15-H), 1.49 (s, 3.6 H, C15-H), 0.86 (s, 3.6 H, C12-H), 0.85 (s, 5.4 H, C12-H), 0.05-0.03 (comp, 3 H, C9-H, C10-H).

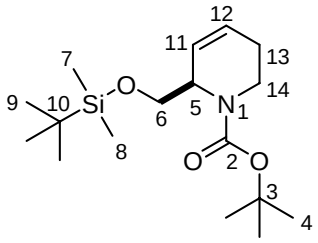


4.102

But-3-enyl-[1-(*tert*-butyldimethylsilanyloxymethyl)allyl]carbamic acid *tert*-butyl ester (4.102) (mp4-057, mp4-058). A mixture of K_2CO_3 (642 mg, 4.65 mmol) and **4.114** (940 mg, 4.65 mmol) in CH_3CN (20 mL), was stirred at room temperature for 30 min. 4-Bromo-1-butene (630 mg, 0.47 mL, 4.65 mmol) was added, and the reaction was heated under reflux overnight. The reaction was allowed to cool to room temperature and the solids were removed by filtration through celite. The solids were rinsed with CH_2Cl_2 (50 mL), and the solvent was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (80 mL) and poured into aqueous saturated $NaHCO_3$ (50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was dissolved in THF (18 mL) and cooled to 0 ˚C. Et_3N (1.25 g, 1.70 mL, 12.3 mmol) was added, and then Boc_2O (1.33 g, 1.30 mL, 6.05 mmol) was added slowly dropwise over 15 min. The ice bath was removed, and the reaction was stirred for 1.5 h, whereupon

additional Boc_2O (0.50 g, 0.50 mL, 2.33 mmol) and DMAP (catalytic amount) were added. The reaction was stirred for 1 h, whereupon the solvent was removed *in vacuo*. The residue was dissolved in Et_2O (100 mL) and poured into 0.5 M HCl (50 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with hexanes / Et_2O (19:1 → 9:1) to give 841 mg (51 %) of **4.102** as a pale yellow oil; ^{1}NMR (500 MHz, DMSO d_6, 100 ˚C) δ 5.91-5.84 (m, 1 H), 5.77 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1 H), 5.18-5.13 (comp, 2 H), 5.04-4.97 (comp, 2 H), 4.25 (app q, *J* = 6.4 Hz, 1 H), 3.80 (dd, *J* = 10.3, 7.5 Hz, 1 H), 3.72 (dd, *J* = 10.3, 5.9 Hz, 1 H), 3.24-3.11 (comp, 2 H), 2.27 (app q, *J* = 7.3 Hz, 1 H), 1.42 (s, 9 H), 0.89 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (125 MHz, DMSO d_6, 100 ˚C) δ 154.1, 135.5, 134.9, 116.1, 115.2, 78.1, 62.8, 60.4, 44.8, 33.0, 27.6, 25.1, 17.2, -6.03, -6.07; IR (neat) 2030, 2858, 1694, 1472, 1409, 1366, 1255, 1175, 1110 cm^{-1} mass spectrum (CI) *m/z* 356.2629 [$C_{19}H_{38}NO_3Si$ (M+1) requires 356.2621], 256, 356 (base).

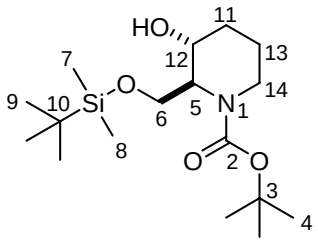
NMR Assignments. ^{1}NMR (500 MHz, DMSO d_6, 100 ˚C) δ 5.91-5.84 (m, 1 H, C11-H), 5.77 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1 H, C15-H), 5.18-5.13 (comp, 2 H, C12-H), 5.04-4.97 (comp, 2 H, C16-H), 4.25 (app q, *J* = 6.4 Hz, 1 H, C5-H), 3.80 (dd, *J* = 10.3, 7.5 Hz, 1 H, C6-H), 3.72 (dd, *J* = 10.3, 5.9 Hz, 1 H, C6-H), 3.24-3.11 (comp, 2 H, C13-H), 2.27 (app q, *J* = 7.3 Hz, 1 H, C14-H), 1.42 (s, 9 H, C4-H), 0.89 (s, 9 H, C9-H), 0.05 (s, 6 H, C7-H, C8-H); ^{13}C NMR (125 MHz, DMSO d_6, 100 ˚C) δ 154.1 (C2), 135.5 (C15), 134.9 (C11), 116.1 (C12), 115.2 (C11), 78.1 (C3), 62.8 (C6), 60.4 (C5), 44.8 (C13), 33.0 (C14), 27.6 (C4), 25.1 (C9), 17.2 (C10), -6.03 (C7 or C8), -6.07 (C7 or C8).



4.101

6-(*tert*-Butyldimethylsilanyloxymethyl)-3,6-dihydro-*2H*-pyridine-1-carboxylic acid *tert*-butyl ester (4.101) (mp4-059). A degassed solution of Grubbs I catalyst (88 mg, 0.11 mmol) and **4.102** (760 mL, 2.14 mmol) in CH_2Cl_2 (45 mL) was stirred at room temperature overnight. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography eluting with hexanes / Et_2O (9:1) to give 524 mg (75 %) of **4.101** as a clear colorless oil; ^{1}NMR (500 MHz, DMSO d_6, 100 ˚C) δ 5.93-5.80 (m, 1 H), 5.73-5.70 (m, 1 H), 4.29 (br s, 1H), 3.98 (dd, *J* = 12.9, 5.6 Hz, 1 H), 3.69-3.63 (comp, 2 H), 3.00-2.89 (m, 1 H), 2.09-1.92 (comp, 2 H), 1.42 (s, 9 H), 0.88 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (125 MHz, DMSO d_6, 100 ˚C) δ 153.3, 125.9, 125.7, 78.1, 63.6, 52.7, 37.1, 27.7, 25.2, 23.9, 17.3, -5.99, -6.02; IR (neat) 2962, 1761, 1521, 1347, 1257, 1217 cm^{-1} mass spectrum (CI) *m/z* 328.2309 [$C_{17}H_{34}NO_3Si$ (M+1) requires 328.2308], 228, 272, 328 (base).

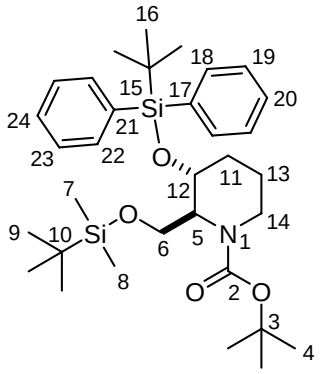
NMR Assignments. ^{1}NMR (500 MHz, DMSO d_6, 100 ˚C) δ 5.93-5.80 (m, 1 H, C12-H), 5.73-5.70 (m, 1 H, C11-H), 4.29 (br s, 1H, C5-H), 3.98 (dd, *J* = 12.9, 5.6 Hz, 1 H, C14-H), 3.69-3.63 (comp, 2 H, C6-H), 3.00-2.89 (m, 1 H, C14-H), 2.09-1.92 (comp, 2 H, C13-H), 1.42 (s, 9 H, C4-H), 0.88 (s, 9 H, C9-H), 0.04 (s, 6 H, C7-H, C8-H); ^{13}C NMR (125 MHz, DMSO d_6, 100 ˚C) δ 153.3 (C2), 125.9 (C12), 125.7 (C11), 78.1 (C3), 63.6 (C6), 52.7 (C5), 37.1 (C14), 27.7 (C4), 25.2 (C9), 23.9 (C13), 17.3 (C10), -5.99 (C7 or C8), -6.02 (C7 or C8).



4.117

2-(*tert*-Butyldimethylsilanyloxymethyl)-4-hydroxypiperidine-1-carboxylic acid *tert*-butyl ester (4.117) (mp4-075). 9-BBN (775 mg, 6.35 mmol) was added to a solution **4.101** (520 mg, 1.59 mmol) in THF (8 mL), and the mixture was heated under reflux for 18 h. The reaction was cooled to 0 ˚C, and a 2 M solution of NaOH (13 mL) and 30% aqueous H_2O_2 (13 mL) were added. The mixture was stirred at 0 ˚C for 1.5, whereupon it was poured into Et_2O (60 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 40 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure to give a residue that was purified by flash chromatography eluting with hexanes / EtOAc (2:1 → 1:1) to give 350 mg (64 %) of **4.117** as a clear colorless oil; ^{1}NMR (500 MHz, DMSO d_6, 100 ˚C) δ 4.20-4.13 (m, 1H), 3.93-3.87 (m, 1 H), 3.77-3.71 (m, 1 H), 3.66-3.56 (comp, 2 H), 3.47-3.40 (m, 1 H), 2.81 (td, *J* = 13.3, 2.8 Hz, 1 H), 2.00-1.95 (m, 1 H), 1.79-1.75 (m, 1 H), 1.40 (s, 9 H), 1.29-1.21 (m, 1 H), 1.19-1.11 (m, 1 H), 0.89 (s, 9 H), 0.05 (s, 6 H, C7-H); ^{13}C NMR (125 MHz, DMSO d_6, 100 ˚C) δ 153.7, 78.0, 62.8, 61.7, 51.9, 31.3, 34.3, 33.9, 27.7, 25.3, 17.3, -6.0; IR (neat) 3440, 2930, 2857, 1693, 1671, 1419, 1365, 1253, 1175 cm^{-1} mass spectrum (CI) *m/z* 346.2418 [$C_{17}H_{36}NO_4Si$ (M+1) requires 346.2414], 246, 290, 346, (base).

NMR Assignments. ^{1}NMR (500 MHz, DMSO d_6, 100 ˚C) δ 4.20-4.13 (m, 1H, C5-H), 3.93-3.87 (m, 1 H, C14-H), 3.77-3.71 (m, 1 H, C12-H), 3.66-3.56 (comp, 2 H, C6-H), 3.47-3.40 (m, 1 H, C14-H), 2.81 (td, *J* = 13.3, 2.8 Hz, 1 H, C14-H), 2.00-1.95 (m, 1 H, C11-H), 1.79-1.75 (m, 1 H, C13-H), 1.40 (s, 9 H, C4-H), 1.29-1.21 (m, 1 H, C11-H), 1.19-1.11 (m, 1 H, C13-H), 0.89 (s, 9 H, C9-H), 0.05 (s, 6 H, C7-H, C8-H); ^{13}C NMR (125 MHz, DMSO d_6, 100 ˚C) δ 153.7 (C2), 78.0 (C3), 62.8 (C12), 61.7 (C6), 51.9 (C5), 31.3 (C14), 34.3 (C13), 33.9 (C11), 27.7 (C4), 25.3 (C9), 17.3 (C10), -6.0 (C7, C8).

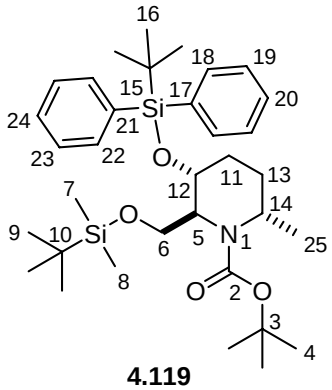


4.118

2-(*tert*-Butyldimethylsilanyloxymethyl)-4-(*tert*-butyldiphenylsilanyloxy)-piperidine-1-caroxylic acid *tert*-butyl ester (4.118) (mp4-076). A solution of *tert*-butyldiphenylchlorosilane (354 mg, 0.34 mL, 1.29 mmol), imidazole (176 mg, 2.59 mmol), and **4.117** (298 mg, 0.86 mmol) in DMF (4.5 mL) was stirred at 50 ˚C overnight. The reaction was allowed to cool to room temperature, and was poured into Et_2O (40 mL). The solution was washed with H_2O (2 x 20 mL) and brine (20 mL), and the organic layer was dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with hexanes / Et_2O (5:1) to give 398 mg (81%) of **4.118** as a clear colorless oil; ^{1}NMR (500 MHz, DMSO d_6, 100 ˚C) δ

7.64-7.59 (comp 4 H), 7.45-7.34 (comp, 6 H), 4.26 (br s, 1H), 4.16-4.13 (m, 1 H), 3.99-3.93 (m, 1 H), 3.59 (dd, J = 10.3, 8.5 Hz, 1 H), 3.48 (dd, J = 10.3, 5.9 Hz, 1 H), 2.80-2.72 (m, 1 H), 1.93-1.84 (m, 1 H), 1.56-1.47 (comp, 2 H), 1.40 (s, 9 H), 1.38-1.32 (m 1 H), 1.06 (s, 9 H), 0.79 (s, 9 H), -0.042 (s, 3 H), -0.046 (s, 3 H); ^{13}C NMR (125 MHz, DMSO d_6, 100 ˚C) δ 154.1, 134.7, 134.6, 133.6, 133.3, 129.08, 129.07, 127.01, 127.00, 77.8, 65.5, 60.3, 58.8, 27.6, 26.4, 25.9, 25.1, 18.4, 18.1, 17.2, -6.14, -6.19; IR (neat) 2930, 2857, 1694, 1111, 838 cm^{-1}; mass spectrum (CI) *m/z* 584.3591 [$C_{33}H_{53}NO_4Si_2$ (M-CH_3) requires 584.3591], 470, 484, 584 (base).

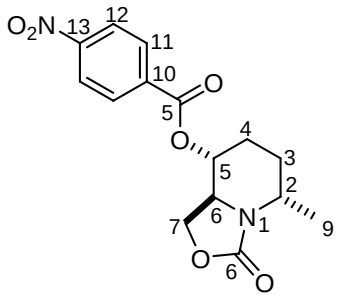
NMR Assignments. ^{1}NMR (500 MHz, DMSO d_6, 100 ˚C) δ 7.64-7.59 (comp 4 H, Ar-H), 7.45-7.34 (comp, 6 H, Ar-H), 4.26 (br s, 1H, C5-H), 4.16-4.13 (m, 1 H, C12-H), 3.99-3.93 (m, 1 H, C14-H), 3.59 (dd, J = 10.3, 8.5 Hz, 1 H, C6-H), 3.48 (dd, J = 10.3, 5.9 Hz, 1 H, C6-H), 2.80-2.72 (m, 1 H, C14-H), 1.93-1.84 (m, 1 H, C13-H), 1.56-1.47 (comp, 2 H, C11-H), 1.40 (s, 9 H, C4-H), 1.38-1.32 (m 1 H, C13-H), 1.06 (s, 9 H, C15-H), 0.79 (s, 9 H, C9-H), -0.042 (s, 3 H, C7-H or C8-H), -0.046 (s, 3 H, C7-H or C8-H); ^{13}C NMR (125 MHz, DMSO d_6, 100 ˚C) δ 154.1 (C2), 134.7 (Ar-C), 134.6 (Ar-C), 133.6 (C17 or C21), 133.3 (C17 or C21), 129.08 (Ar-C), 129.07 (Ar-C), 127.01 (Ar-C), 127.00 (Ar-C), 77.8 (C3), 65.5 (C12), 60.3 (C6), 58.8 (C5), 27.6 (C4), 26.4 (C15), 25.9 (C11), 25.1 (C9), 18.4 (C10 or C16), 18.1 (C13), 17.2 (C10 or C16), -6.14 (C7 or C8), -6.19 (C7 or C8).



4.119

2-(*tert*-Butyldimethylsilanyloxymethyl)-4-(*tert*-butyldiphenylsilanyloxy)-6-methylpiperidine-1-carboxylic acid *tert*-butyl ester (4.119) (mp4-079-1). *N*,*N*.*N*',*N*'-Tetramethylethylenediamine (TMEDA) (73 mg, 94 μL, 0.63 mmol) was added to a solution **4.118** (270 mg, 0.47 mmol) in Et_2O (1.9 mL) at –78 ˚C. A solution of *sec*-BuLi (0.47 mL, 0.63 mmol, 1.34 M) in hexanes was added dropwise, and the mixture was stirred at –78 ˚C for 2 h and 45 min, whereupon MeI (201 mg, 88 μL, 1.4 mmol) was added. The cold bath was removed, and the reaction was stirred for 1 h, whereupon H_2O (2 mL) was added. The mixture was poured into a separatory funnel containing Et_2O (20 mL) and H_2O (20 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 20 mL). The combined organic extracts were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with hexanes / Et_2O (5:1) to give 150 mg (54%) of **4.119** as a clear colorless oil. **NMR Assignments.** ^{1}NMR (400 MHz, $CDCl_3$) δ 7.66-7.63 (comp 4 H), 7.41-7.31 (comp, 6 H), 4.29-24 (m, 1H), 4.08-4.02 (m, 1 H), 3.88-3.80 (m, 1 H), 3.47 (dd, J = 9.4, 4.6 Hz, 1 H), 3.38 (app t, J = 9.4, Hz, 1 H), 1.81-1.59 (comp, 4 H), 1.49 (d, J = 6.5 Hz, 3 H), 1.45 (s, 9 H), 1.06 (s, 9 H), 0.72 (s, 9 H), -0.13 (s, 6 H); IR (neat) 2930, 2857, 1692, 1365, 1111, 838 cm^{-1}.

NMR Assignments. ^{1}NMR (400 MHz, $CDCl_3$) δ 7.66-7.63 (comp 4 H, Ar-H), 7.41-7.31 (comp, 6 H, Ar-H), 4.29-24 (m, 1H, C5-H), 4.08-4.02 (m, 1 H, C12-H), 3.88-3.80 (m, 1 H, C14-H), 3.47 (dd, *J* = 9.4, 4.6 Hz, 1 H, C6-H), 3.38 (app t, *J* = 9.4, Hz, 1 H, C6-H), 1.81-1.59 (comp, 4 H, C4-H), 1.49 (d, *J* = 6.5 Hz, 3 H, C15-H), 1.45 (s, 9 H, C4-H), 1.06 (s, 9 H, C17-H), 0.72 (s, 9 H, C9-H), -0.13 (s, 6 H, C7-H, C8-H).

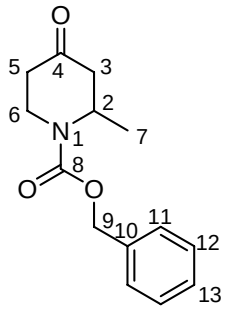


4.121

2-(*tert*-Butyldimethylsilanyloxymethyl)-4-(*tert*-butyldiphenylsilanyloxy)-6-methylpiperidine-1-carboxylic acid *tert*-butyl ester (4.121) (mp4-078, mp4-080). TBAF (336 mg, 1.28 mmol) was added to a solution of **4.119** (150 mg, 0.26 mmol) in THF (2.6 mL), and the reaction was stirred at room temperature 1.3 h. The reaction was poured into H_2O (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc / hexanes (1:1 → 2:1) to give 56 mg (89%) of **4.120** as a clear colorless oil. DMAP (53 mg, 0.44 mmol) and *p*NO_2BzCl (85 mg, 0.46 mmol) were added to a solution of **4.120** (56 mg, 0.22 mmol) in CH_2Cl_2 (2.3 mL), and the reaction was stirred at room temperature 1.5 h. The reaction was cooled to 0 °C and Et_3N (0.06 mL, 0.44 mmol) and *p*NO_2BzCl (85 mg, 0.46 mmol) were added. The reaction was stirred for 30 min at 0 °C, whereupon it was poured into H_2O (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts

were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc / hexanes (1:1) to give 32 mg (46%) of **4.121** as a white crystalline solid: mp 182-183 °C; ^{1}NMR (500 MHz, $CHCl_3$) δ 8.27 (d, *J* = 9.3 Hz, 2 H), 7.37 (d, *J* = 9.3 Hz, 2 H), 4.57-4.52 (m, 1 H), 4.44 (dd, *J* = 9.2, 8.0 Hz, 1 H), 4.21 (dd, *J* = 9.2, 5.5 Hz, 1 H), 4.19-4.14 (m, 1 H), 3.86 (ddd, *J* = 9.7, 8.0, 5.5 Hz, 1 H), 2.24-2.19 (m, 1 H), 1.92-1.78 (comp, 2 H), 1.71-1.66 (m, 1 H), 1.25 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CHCl_3$) δ 156.2, 155.1, 151.7, 145.6, 125.4, 121.6, 77.6, 66.1, 53.3, 44.3, 27.9, 24.2, 15.9; IR (neat) 2947, 1761, 1521, 1259, 1217, 1057 cm^{-1} mass spectrum (CI) *m/z* 321.1089 [$C_{15}H_{17}N_2O_6$ (M+1) requires 321.1087], 307 (base), 321, 325.

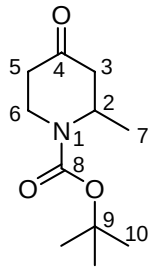
NMR Assignments. ^{1}NMR (500 MHz, $CHCl_3$) δ 8.27 (d, *J* = 9.3 Hz, 2 H, C13-H), 7.37 (d, *J* = 9.3 Hz, 2 H, C12-H), 4.57-4.52 (m, 1 H, C5-H), 4.44 (dd, *J* = 9.2, 8.0 Hz, 1 H, C7-H), 4.21 (dd, *J* = 9.2, 5.5 Hz, 1 H, C7-H), 4.19-4.14 (m, 1 H, C2-H), 3.86 (ddd, *J* = 9.7, 8.0, 5.5 Hz, 1 H, C6-H), 2.24-2.19 (m, 1 H, C4-H), 1.92-1.78 (comp, 2 H, C3-H, C4-H), 1.71-1.66 (m, 1 H, C3-H), 1.25 (d, *J* = 7.0 Hz, 3 H, C9-H); ^{13}C NMR (125 MHz, $CHCl_3$) δ 156.2 (C10 or C8), 155.1 (C10 or C8), 151.7 (C14), 145.6 (C11), 125.4 (C13), 121.6 (C12), 77.6 (C5), 66.1 (C7), 53.3 (C6), 44.3 (C2), 27.9 (C3), 24.2 (C4), 15.9 (C9).



4.132

2-Methyl-4-oxopiperidine-1-carboxylic acid benzyl ester (4.132) (mp4-100). CBz-Cl (2.80 mL, 19.7 mmol) was added to a solution of **4.130** (2.00 mL, 19.7 mmol) in THF (100 mL) at –25 °C. The reaction was stirred at –25 °C for 20 min, whereupon a solution of methyl magnesium bromide (7.80 mL, 3 M, 23.6 mmol) in ether was added. The reaction was stirred at –25 °C for 30 min, whereupon the cold bath was removed, and stirring was continued for 40 min. A 3 M aqueous solution of HCl (40 mL) was added, and stirring was continued for 20 min. The slurry was extracted with Et_2O (3 x 40 mL), and the combined organic phases were dried (Na_2SO_4). The solvent was removed under reduced pressure. The residue was dissolved in THF (75 mL), cooled to –78 °C, and a solution of L-selectride (16.5 mL, 1 M, 16.5 mmol) in THF was added. The reaction was stirred at –78 °C for 15 min, whereupon the cold bath was removed, and stirring was continued for 45 min. Water (4 mL) was added, and the volatiles were removed under reduced pressure. The residue was dissolved in water (100 mL) and the aqueous solution was extracted with EtOAc (2 x 100 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with hexanes / EtOAc (7:3) to give 3.09 g (61 %, 2 steps) of **4.132** as a clear colorless oil; ^{1}NMR (500 MHz, $CDCl_3$) δ 7.38-7.28 (comp, 5 H), 5.15 (s, 2 H), 5.48-4.75 (m, 1 H), 4.34-4.25 (m, 1 H), 3.37 (ddd, *J* = 14.0, 11.3, 4.1 Hz, 1 H), 2.66 (dd, *J* = 14.7, 6.8 Hz, 1 H), 2.47 (ddd, *J* = 15.4, 11.3, 6.8 Hz, 1 H), 2.36-2.31 (m, 1 H), 2.27-2.22 (m, 1H), 1.18 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.0, 155.3, 136.6, 128.8, 128.5, 128.2, 67.8, 48.5, 46.8, 40.8, 39.0, 38.8. 19.0; IR (neat) 2966, 1698, 1419, 1331, 1219, 1185, 1120, 1066 cm^{-1}; mass spectrum (HRMS:CI; LRMS:ESI) *m/z* 248.1291 [$C_{14}H_{18}NO_3$ (M+1) requires 248.1287] 242, 248, 265 (base), 384.

NMR Assignments. ^{1}NMR (500 MHz, $CDCl_3$) δ 7.38-7.28 (comp, 5 H, Ar-H), 5.15 (s, 2 H, C9-H), 5.48-4.75 (m, 1 H, C2-H), 4.34-4.25 (m, 1 H, C6-H), 3.37 (ddd, *J* = 14.0, 11.3, 4.1 Hz, 1 H, C6-H), 2.66 (dd, *J* = 14.7, 6.8 Hz, 1 H, C3-H), 2.47 (ddd, *J* = 15.4, 11.3, 6.8 Hz, 1 H, C5-H), 2.36-2.31 (m, 1 H, C5-H), 2.27-2.22 (m, 1H, C3-H), 1.18 (d, *J* = 6.8 Hz, 3 H, C7-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.0 (C4), 155.3 (C8), 136.6 (C10), 128.8 (Ar-C), 128.5 (Ar-C), 128.2 (Ar-C), 67.8 (C9), 48.5 (C2 or C3 or C5 or C6), 46.8 (C2 or C3 or C5 or C6), 40.8 (C2 or C3 or C5 or C6), 39.0 (C2 or C3 or C5 or C6), 38.8 (C7).

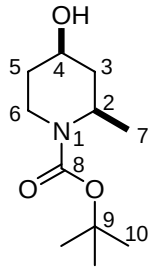


4.133

2-Methyl-4-oxopiperidine-1-carboxylic acid *tert*-butyl ester (4.133) (mp4-101). A solution of **4.132** (3.09 g, 11.7 mmol) and 10 wt % Pd/C (300 mg) in EtOH (60 mL) was stirred at room temperature over night, whereupon Boc_2O (3.7 mL, 17.5 mmol) was added. The reaction was stirred for an additional 2 h and filtered through celite. The solids were washed with EtOH (20 mL) and filtrate and washings were removed under reduced pressure. The residue was purified by flash chromatography eluting with hexanes / EtOAc (8:2 → 7:3) to give 2.20 g (77%) of **4.133** as a clear colorless oil; ^{1}NMR (500 MHz, $CDCl_3$) δ 4.66-4.61 (m, 1 H), 4.20 (ddd, *J* = 13.7, 6.8, 2.7 Hz, 1 H), 3.28 (ddd, *J* = 13.7, 11.3, 3.8 Hz, 1 H), 2.65 (dd, *J* = 14.4, 6.8 Hz, 1 H), 2.45 (ddd, *J* = 15.4, 11.3, 6.8 Hz, 1 H), 2.34-2.27 (m, 1 H), 2.22 (ddd, *J* = 14.4, 2.7, 1.7 Hz, 1 H), 1.46 (s, 9 H), 1.15 (d,

J = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.7, 154.7, 80.5, 46.8, 40.8, 39.9, 38.3, 30.0, 28.6; IR (neat) 2975, 1693, 1404, 1366, 1249, 1165 cm^{-1}; mass spectrum (HRMS:CI; LRMS:ESI) *m/z* 214.1447 [$C_{11}H_{19}NO_3$ (M+1) requires 214.1443] 214, 236, 242 (base), 265.

NMR Assignments. ^{1}NMR (500 MHz, $CDCl_3$) δ 4.66-4.61 (m, 1 H, C2-H), 4.20 (ddd, *J* = 13.7, 6.8, 2.7 Hz, 1 H, C6-H), 3.28 (ddd, *J* = 13.7, 11.3, 3.8 Hz, 1 H, C6-H), 2.65 (dd, *J* = 14.4, 6.8 Hz, 1 H, C3-H), 2.45 (ddd, *J* = 15.4, 11.3, 6.8 Hz, 1 H, C5-H), 2.34-2.27 (m, 1 H, C5-H), 2.22 (ddd, *J* = 14.4, 2.7, 1.7 Hz, 1 H, C3-H), 1.46 (s, 9 H, C10-H), 1.15 (d, *J* = 6.8 Hz, 3 H, C7-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.7 (C4), 154.7 (C8), 80.5 (C9), 46.8 (C3), 40.8 (C2 or C5 or C6), 39.9 (C2 or C5 or C6), 38.3 (C2 or C5 or C6), 30.0 (C7), 28.6 (C10).

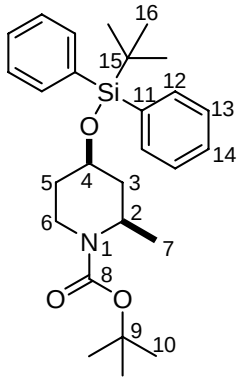


4.134

4-Hydroxy-2-methylpiperidine-1-carboxylic acid *tert*-butyl ester (4.134) (mp4-107). A solution of L-selectride (5.20 mL, 1 M, 5.16 mmol) in THF was added to a solution of **4.133** (1.10 g, 4.48 mmol) in THF (80 mL) at −78 °C. The reaction was stirred at −78 °C for 10 min, whereupon MeOH (10 mL) was added, and the cold bath was removed. Stirring was continued for 40 min, the reaction was poured into a separatory funnel containing water (200 mL) and the aqueous mixture was extracted with CH_2Cl_2 (200 mL and 2 x 100 mL). The combined organic layers were washed with brine (50 mL) and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The

residue was purified by flash chromatography eluting with hexanes / EtOAc (3:1 → 2:1) to give 837 mg (75 %) of **4.134** as a clear colorless oil; ^{1}NMR (500 MHz, $CDCl_3$) δ 4.25 (pent d, *J* = 7.0, 1.8 Hz, 1 H), 4.13 (pent, *J* = 3.3 Hz, 1 H), 3.78 (ddd, *J* = 13.6, 4.5, 2.8 Hz, 1H), 3.22 (ddd, *J* = 13.6, 12.0, 4.0 Hz, 1 H), 1.81 (ddd, *J* = 14.5, 6.8, 3.3 Hz, 1 H), 1.72-1.55 (comp, 3 H), 1.43 (s, 9 H), 1.29 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 79.2, 64.9, 45.4, 36.4, 33.2, 32.4, 28.5, 19.1; IR (neat) 3436, 2972, 2930, 1691, 1665, 1419, 1365, 1173, 1078 cm^{-1};

NMR Assignments. ^{1}NMR (500 MHz, $CDCl_3$) δ 4.25 (pent d, *J* = 7.0, 1.8 Hz, 1 H, C2-H), 4.13 (pent, *J* = 3.3 Hz, 1 H, C4-H), 3.78 (ddd, *J* = 13.6, 4.5, 2.8 Hz, 1H, C6-H), 3.22 (ddd, *J* = 13.6, 12.0, 4.0 Hz, 1 H, C6-H), 1.81 (ddd, *J* = 14.5, 6.8, 3.3 Hz, 1 H, C3-H), 1.72-1.55 (comp, 3 H, C3-H, C5-H), 1.43 (s, 9 H, C10-H), 1.29 (d, *J* = 7.0 Hz, 3 H, C7-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9 (C8), 79.2 (C9), 64.9 (C4), 45.4 (C2), 36.4 (C3), 33.2 (C6), 32.4 (C5), 28.5 (C10), 19.1 (C7).

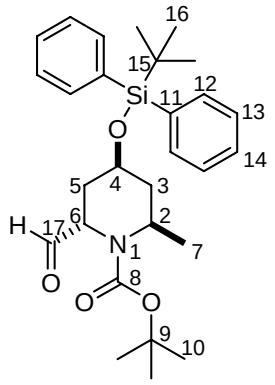


4.135

4-(*tert*-Butyldiphenylsilanyloxy)-2-methylpiperidine-1-carboxylic acid *tert*-butyl ester (4.135) (mp4-109). A solution of **4.134** (837 mg, 3.38 mmol), TBDPSCl (1.32 mL, 5.08 mmol) and imidazole (690 mg, 10.1 mmol) in DMF (17 mL) was heated at 50 °C overnight. The reaction was allowed to cool to room temperature, whereupon it

was diluted with Et_2O (200 mL). The solution was washed with H_2O (2 x 100 mL), 0.5 M aqueous HCl (100 mL), and brine (100 mL), and the organic layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with hexanes / EtOAc (3:1 → 2:1) to give 837 mg (75 %) of **4.135** as a clear colorless oil; ^{1}NMR (500 MHz, $CDCl_3$) δ 7.66-7.62 (comp, 4 H), 7.44-7.39 (comp, 2 H), 7.38-7.33 (comp, 4 H), 4.30-4.23 (m, 1 H), 4.08 (pent, *J* = 3.1 Hz, 1 H), 3.78 (ddd, *J* = 13.2, 4.4, 2.4 Hz, 1 H), 3.35 (td, *J* = 13.2, 3.0, Hz, 1 H), 1.64-1.61 (comp, 2 H), 1.49-1.34 (comp, 2 H), 1.43 (s, 9 H), 1.42 (d, *J* = 7.1 Hz), 1.07 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 135.8, 134.04, 133.95, 129.7, 127.6, 79.1, 66.2, 45.6, 36.3, 33.4, 32.5, 28.5, 27.0, 19.3, 19.1; IR (neat) 2963, 2858, 1692, 1412, 1363, 1174, 1111, 1053, 702 cm^{-1}.

NMR Assignments. ^{1}NMR (500 MHz, $CDCl_3$) δ 7.66-7.62 (comp, 4 H, Ar-H), 7.44-7.39 (comp, 2 H, Ar-H), 7.38-7.33 (comp, 4 H, Ar-H), 4.30-4.23 (m, 1 H, C2-H), 4.08 (pent, *J* = 3.1 Hz, 1 H, C4-H), 3.78 (ddd, *J* = 13.2, 4.4, 2.4 Hz, 1 H, C6-H), 3.35 (td, *J* = 13.2, 3.0, Hz, 1 H, C6-H), 1.64-1.61 (comp, 2 H, C3-H), 1.49-1.34 (comp, 2 H, C5-H), 1.43 (s, 9 H, C10-H), 1.42 (d, *J* = 7.1 Hz, 3 H, C7-H), 1.07 (s, 9 H, C16-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0 (C8), 135.8 (Ar-C), 134.04 (Ar-C), 133.95 (Ar-C), 129.7 (Ar-C), 127.6 (Ar-C), 79.1 (C9), 66.2 (C4), 45.6 (C2), 36.3 (C3), 33.4 (C6), 32.5 (C5), 28.5 (C10), 27.0 (C16), 19.3 (C7 or C15), 19.1 (C7 or C15).

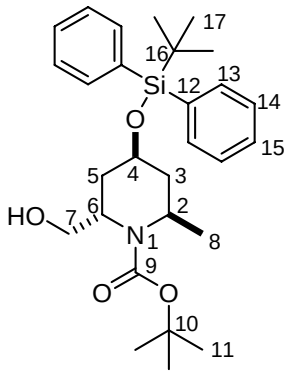


4.136

4-(*tert*-Butyldiphenylsilanyloxy)-2-formyl-6-methylpiperidine-1-carboxylic acid *tert*-butyl ester (4.136) (mp4-113) A solution of *sec*-BuLi (3.10 mL, 1.39 M, 4.27 mmol) in cyclohexane was added dropwise over 15 min to a solution of **4.135** (1.49 g, 3.28 mmol) and tetramethylethylenediamine (TMEDA) (0.64 mL, 4.27 mmol) in Et_2O (13 mL) at −78 °C. The solution was stirred at −78 °C for 1 h, whereupon DMF (0.51 mL, 6.56 mmol) was added. Stirring was continued at −78 °C for 1 h, and a saturated aqueous solution of NH_4Cl (8 mL) was added. The cold bath was removed, and the slurry was allowed to warm to room temperature and poured into a separatory funnel containing H_2O (75 mL). The mixture was extracted with EtOAc (3 x 75 mL), and the combined organic layers were dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with hexanes / EtOAc (10:1) to give 1.47 g (92%, *dr* = 94:6) of **4.136** as a pale yellow oil; ^{1}NMR (500 MHz, $CDCl_3$) δ 9.34 (d, *J* = 2.8 Hz, 1 H), 7.65-7.60 (comp, 4 H), 7.44-7.39 (comp, 2 H), 7.38-7.34 (comp, 4 H), 4.23-4.16 (m, 1 H), 4.12 (app pent, *J* = 3.5 Hz, 1 H), 4.07 (td, *J* = 10.7, 3.3, Hz, 1 H), 1.74-1.68 (m, 1 H), 1.65-1.61 (comp, 2 H), 1.57-1.42 (m, 1 H), 1.45 (d, *J* = 6.9 Hz, 3 H), 1.43 (s, 9 H), 1.06 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.7, 156.1, 135.77, 135.75, 133.6, 133.3, 129.9, 129.8, 127.75, 127.68, 81.3, 65.0, 55.9, 47.3, 36.0,

32.5, 28.2, 27.0, 20.2, 12.0; IR (neat) 2965, 2991, 1732, 1683, 1367, 1302, 1104, 702 cm^{-1}; mass spectrum (ESI) *m/z* 482.2706 [$C_{28}H_{39}NO_4Si$ (M+1) requires 482.2721].

NMR Assignments. ^{1}NMR (500 MHz, $CDCl_3$) δ 9.34 (d, *J* = 2.8 Hz, 1 H, C17-H), 7.65-7.60 (comp, 4 H, Ar-H), 7.44-7.39 (comp, 2 H, Ar-H), 7.38-7.34 (comp, 4 H, Ar-H), 4.23-4.16 (m, 1 H, C2-H), 4.12 (app pent, *J* = 3.5 Hz, 1 H, C4-H), 4.07 (td, *J* = 10.7, 3.3, Hz, 1 H, C6-H), 1.74-1.68 (m, 1 H, C5-H), 1.65-1.61 (comp, 2 H, C3-H), 1.57-1.42 (m, 1 H, C5-H), 1.45 (d, *J* = 6.9 Hz, 3 H, C7-H), 1.43 (s, 9 H, C10-H), 1.06 (s, 9 H, C16-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.7 (C17), 156.1 (C8), 135.77 (Ar-C), 135.75 (Ar-C), 133.6 (Ar-C), 133.3 (Ar-C), 129.9 (Ar-C), 129.8 (Ar-C), 127.75 (Ar-C), 127.68 (Ar-C), 81.3 (C9), 65.0 (C4), 55.9 (C6), 47.3 (C2), 36.0 (C3), 32.5 (C5), 28.2 (C10), 27.0 (C16), 20.2 (C7), 12.0 (C16).

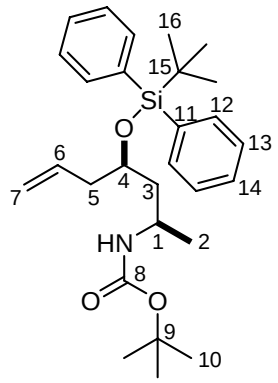


4.137

4-(*tert*-Butyldiphenylsilanyloxy)-2-hydroxymethyl-6-methylpiperidine-1-carboxylic acid *tert*-butyl ester (4.137) (mp4-114). $NaBH_4$ (459 mg, 12.1 mmol) was added to a solution of **4.136** (1.46 g, 3.03 mmol) in MeOH (30 mL) at 0 °C. The reaction was stirred at 0 °C for 1 h and 15 min, whereupon a saturated aqueous solution of NH_4Cl (10 mL) was added. The mixture was poured into H_2O (100 mL), and the mixture was extracted with EtOAc (3 x 100 mL). The organic layer was dried (Na_2SO_4), and the

solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with hexanes / EtOAc (4:1) to give 1.33 g (91 %) of **4.137** as a clear colorless oil; ^{1}NMR (500 MHz, $CDCl_3$) δ 7.65-7.60 (comp, 4 H), 7.43-7.39 (comp, 2 H), 7.38-7.33 (comp, 4 H), 4.15-4.07 (comp, 2 H), 3.93 (app hept, *J* = 3.7 Hz, 1 H), 3.63-3.55 (comp, 2 H), 1.80-1.74 (comp, 2 H), 1.72-1.67 (m, 1 H), 1.63-1.59 (m, 1 H), 1.44 (d, *J* = 7.1 Hz, 3 H), 1.42 (s, 9 H), 1.05 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 135.8, 135.7, 133.9, 129.8, 129.7, 127.65, 127.64, 80.1, 65.8, 65.6, 51.3, 48.2, 36.9, 34.8, 28.4, 26.9, 20.8, 19.0; IR (neat) 3435, 2963, 2932, 1683, 1428, 1322, 1366, 1111, 1072, 702 cm^{-1}; mass spectrum (ESI) *m/z* 484.2895 [$C_{28}H_{42}NO_4Si$ (M+1) requires 484.2878].

NMR Assignments. ^{1}NMR (500 MHz, $CDCl_3$) δ 7.65-7.60 (comp, 4 H, Ar-H), 7.43-7.39 (comp, 2 H, Ar-H), 7.38-7.33 (comp, 4 H, Ar-H), 4.15-4.07 (comp, 2 H, C4-H, C2-H), 3.93 (app hept, *J* = 3.7 Hz, 1 H, C6-H), 3.63-3.55 (comp, 2 H, C7-H), 1.80-1.74 (comp, 2 H, C5-H, C3-H), 1.72-1.67 (m, 1 H, C5-H or C3-H), 1.63-1.59 (m, 1 H, C5-H or C3-H), 1.44 (d, *J* = 7.1 Hz, 3 H, C8-H), 1.42 (s, 9 H, C11-H), 1.05 (s, 9 H, C17-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2 (C9), 135.8 (Ar-C), 135.7 (Ar-C), 133.9 (Ar-C), 129.8 (Ar-C), 129.7 (Ar-C), 127.65 (Ar-C), 127.64 (Ar-C), 80.1 (C10), 65.8 (C7), 65.6 (C2), 51.3 (C6), 48.2 (C4), 36.9 (C5 or C3), 34.8 (C5 or C3), 28.4 (C11), 26.9 (C17), 20.8 (C8), 19.0 (C16).

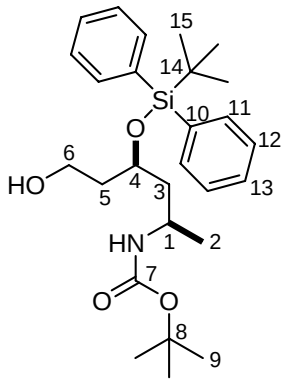


4.139

[3-(tert-Butyldiphenylsilanyloxy)-1-methylhex-5-enyl)-3-carbamic acid *tert*-butyl ester (4.139) (mp4-242 and mp4-241). A solution of allylmagnesium bromide (16.0 mL, 1.0 M, 16.0 mmol) was added to a stirred solution of (-)-DIP-Cl (6.00 g, 18.7 mmol) in Et_2O (93 mL) at –78 ˚C. The reaction was stirred at –78 ˚C for 5 min, whereupon the cold bath was replaced with an ice water bath, and the mixture was stirred for 1 h. The reaction was cooled to –78 ˚C, whereupon a solution of aldehyde **4.138** (2.50 g, 13.4 mmol) in Et_2O (25 mL, and 5 mL rinse) was added dropwise via cannula over 20 min. Stirring was continued at –78 ˚C for 1 h, whereupon a saturate aqueous solution of $NaHCO_3$ (20 mL) was added. The cold bath was removed, and stirring was continued for 30 min. The reaction was poured into a separatory funnel containing saturated aqueous $NaHCO_3$ (300 mL), and the mixture was extracted with Et_2O (3 x 300 mL). The combined organic extracts were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes / EtOAc (3:1) to give a clear colorless oil, which was redissolved in DMF (54 mL). TBDPSCl (4.80 mL, 18.3 mmol) and imidazole (2.35 g, 34.5 mmol) were added and the reaction was stirred at 50 ˚C overnight. The reaction was diluted with Et_2O (400 mL), and the solution was washed with H_2O (2 x 200 mL), 0.5 M aqueous HCl (200 mL)

and brine (200 mL). The organic layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with hexanes / EtOAc (9:1) to give 1.92 g (31%, 2 steps) of **4.139** as a clear colorless oil; ^{1}NMR (500 MHz) δ 7.71-7.66 (comp, 4 H), 7.44-7.34 (comp, 6 H), 5.60-5.51 (m, 1 H), 4.92-4.82 (comp, 2 H), 3.85-3.81 (comp, 1 H), 3.73-3.65 (m, 1 H), 2.23-2.16 (m, 1 H), 2.15-2.09 (comp, 1 H), 1.68-1.60 (m, 1 H), 1.54-1.47 (m, 1 H), 1.42 (s, 9 H), 1.05 (s, 9 H), 1.02 (d, *J* = 6.35 Hz, 3 H); ^{13}C NMR (125 MHz) δ 155.3, 135.91, 135.88, 134.8, 134.25, 134.18, 133.6, 129.7, 129.6, 127.6, 127.5, 117.4, 78.8, 71.3, 43.9, 41.9, 40.8, 28.5, 27.0, 21.6, 19.3; IR (neat) 3430, 2965, 2931, 1703, 1501, 1365, 1174, 1112, 1054 cm^{-1}; mass spectrum (CI) *m/z* 468.2934 [$C_{28}H_{42}NO_3Si$ (M+1) requires 468.2934], 231, 305, 335, 468 (base).

NMR Assignments. ^{1}NMR (500 MHz) δ 7.71-7.66 (comp, 4 H, Ar-H), 7.44-7.34 (comp, 6 H, Ar-H), 5.60-5.51 (m, 1 H, C6-H), 4.92-4.82 (comp, 2 H, C7-H), 3.85-3.81 (comp, 1 H, C4-H), 3.73-3.65 (m, 1 H, C1-H), 2.23-2.16 (m, 1 H, C6-H), 2.15-2.09 (comp, 1 H, C6-H), 1.68-1.60 (m, 1 H, C3-H), 1.54-1.47 (m, 1 H, C3-H), 1.42 (s, 9 H, C10-H), 1.05 (s, 9 H, C16-H), 1.02 (d, *J* = 6.35 Hz, 3 H, C2-H); ^{13}C NMR (125 MHz) δ 155.3 (C8), 135.91 (Ar-C), 135.88 (Ar-C), 134.8 (Ar-C), 134.25 (C6), 134.18 (Ar-C), 133.6 (C6), 129.7 (Ar-C), 129.6 (Ar-C), 127.6 (Ar-C), 127.5 (Ar-C), 117.4 (C7), 78.8 (C9), 71.3 (C4), 43.9 (C1), 41.9 (C3), 40.8 (C6), 28.5 (C10), 27.0 (C16), 21.6 (C2), 19.3 (C15).

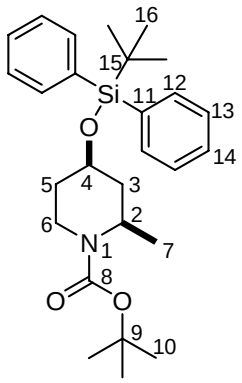


4.140

[3-(*tert*-Butyldiphenylsilanyloxy)-5-hydroxy-1-methylpentyl]-carbamic acid *tert*-butyl ester (4.140) (mp4-244). A stream of ozone was passed through a solution of **4.139** (1.20 g, 2.56 mmol) at –78 ˚C for 10 min. The blue solution was then sparged with N_2 for 15 min, whereupon $NaBH_4$ (970 mg, 25.6 mmol) was added and the cold bath removed. Stirring was continued for 25 min, and a saturated aqueous solution of NH_4Cl (30 mL) was added. The volatiles were removed under reduced pressure, and the remaining aqueous residue was diluted with brine (100 mL). The resulting slurry was extracted with EtOAc (3 x 400 mL) and washed with H_2O (2 x 200 mL), 0.5 M aqueous HCl (200 mL, and brine (200 mL). The organic layer was dried (Na_2SO_4), the solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with hexanes / EtOAc (2:1 → 1:1) to give 1.07 g (88%) of **4.140** as a clear colorless oil; ^{1}NMR (500 MHz) δ 7.70-7.68 (comp, 4 H), 7.44-7.34 (comp, 6 H), 4.63 (br s, 1 H), 3.99-3.94 (m, 1 H), 3.70-3.57 (comp, 2 H), 3.52-3.42 (m, 1 H), 1.85-1.73 (comp, 2 H), 1.70-1.64 (m, 1 H), 1.46-1.36 (m, 1 H), 1.39 (s, 9 H), 1.04 (s, 9 H), 0.84 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR (125 MHz) δ 155.2, 135.92, 135.88, 133.6, 129.9, 129.8, 127.70, 129.69, 70.0, 59.4, 43.9, 42.9, 37.8, 28.4, 27.0, 20.9, 19.2; IR (neat) 3351,

2964, 2931, 1692, 1504, 1427, 1366, 1173, 1111, 1060 cm^{-1}; mass spectrum (CI) *m/z* 472.3886 [$C_{27}H_{42}NO_4Si$ (M+1) requires 472.2883], 315, 373, 472 (base).

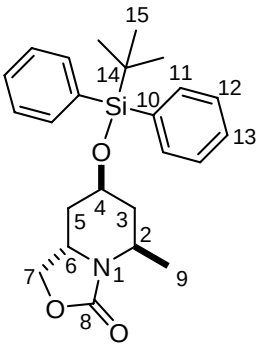
NMR Assignments. ^{1}NMR (500 MHz) δ 7.70-7.68 (comp, 4 H, Ar-H), 7.44-7.34 (comp, 6 H, Ar-H), 4.63 (br s, 1 H, NH), 3.99-3.94 (m, 1 H, C4-H), 3.70-3.57 (comp, 2 H, C6-H), 3.52-3.42 (m, 1 H, C1-H), 1.85-1.73 (comp, 2 H, C3-H or C5-H, OH), 1.70-1.64 (m, 1 H, C3-H or C5-H), 1.46-1.36 (m, 1 H, C3-H or C5-H), 1.39 (s, 9 H, C15-H), 1.04 (s, 9 H, C16-H), 0.84 (d, *J* = 6.3 Hz, 3 H, C2-H); ^{13}C NMR (125 MHz) δ 155.2 (C8), 135.92 (Ar-C), 135.88 (Ar-C), 133.6 (Ar-C), 129.9 (Ar-C), 129.8 (Ar-C), 127.70 (Ar-C), 129.69 (Ar-C), 70.0 (C4), 59.4 (C6), 43.9 (C1), 42.9 (C3 or C5), 37.8 (C3 or C5), 28.4 (C9), 27.0 (C15), 20.9 (C2), 19.2 (C15).



4.135

4-(*tert*-Butyldiphenylsilanyloxy)-2-methylpiperidine-1-carboxylic acid *tert*-butyl ester (4.135) (mp4-237, mp4-235). MsCl (29 μL, 0.29 mmol) was added to a solution **4.140** (69 mg, 0.15 mmol) and Et_3N (45 μL) in CH_2Cl_2 (1.8 mL) and stirred at room temperature for 30 min. The mixture was poured into a separatory funnel containing H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with hexanes / EtOAc (2:1) to give

69 mg (88 %) of **4.141** as a yellow oil. KO*t*Bu (12 mg, 0.11 mmol) was added to a solution **4.141** (30 mg, 0.05 mmol) in THF (1.1 mL) at 0 ˚C, and the reaction was stirred at 0 ˚C for 20 min, whereupon a saturated aqueous solution of NH_4Cl (1 mL) was added. The mixture was poured into a separatory funnel containing H_2O (10 mL), and the aqueous mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with hexanes / EtOAc (8:1) to give 24 mg (98 %) of **4.135** as a clear colorless oil; The ^1H NMR spectrum was identical to that previously reported (*vide supra*).

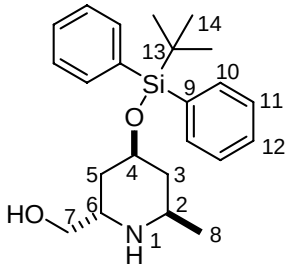


4.143

7-(*tert*-Butyldiphenylsilanyl)-5-methylhexahydrooxazolo[3,4-a]pyridin-3-one (4.143) (mp4-106). MsCl (14 μL, 0.18 mmol) was added to a solution of **4.137** (44 mg, 0.09 mmol) and Et_3N (38 μL, 0.27 mmol) in CH_2Cl_2 (0.9 mL) at 0 °C. The reaction was stirred at 0 °C for 1 h, whereupon a saturated aqueous solution of NH_4Cl (1 mL) was added. The mixture was poured into H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with 0.5 M HCl (5 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was recrystallized from Et_2O/heptane to give 19 mg (51%) of **4.143** as a white solid; ^{1}NMR

(400 MHz, $CHCl_3$) δ 7.64-7.61 (comp, 4 H), 7.46-7.34 (comp, 6 H), 4.40 (app t, *J* = 8.2 Hz, 1 H), 4.31-4.21 (comp, 2 H), 4.13-4.05 (m, 1 H), 3.77 (dd, *J* = 8.2, 6.2 Hz, 1 H), 1.73-1.59 (comp, 3 H), 1.50 (d, *J* = 7.2 Hz, 3 H), 1.30-1.20 (m, 1 H), 1.08 (s, 9 H).

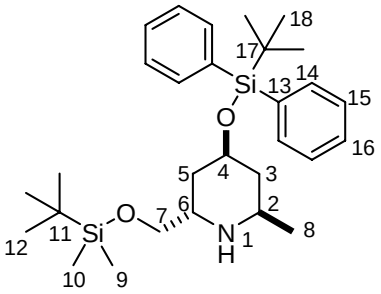
NMR Assignments. ^{1}NMR (400 MHz, $CHCl_3$) δ 7.64-7.61 (comp, 4 H, Ar-H), 7.46-7.34 (comp, 6 H, Ar-H), 4.40 (app t, *J* = 8.2 Hz, 1 H, C7-H), 4.31-4.21 (comp, 2 H, C4-H, C6-H), 4.13-4.05 (m, 1 H, C2-H), 3.77 (dd, *J* = 8.2, 6.2 Hz, 1 H, C6-H), 1.73-1.59 (comp, 3 H, C3-H, C5-H), 1.50 (d, *J* = 7.2 Hz, 3 H, C9-H), 1.30-1.20 (m, 1 H, C3-H or C5-H), 1.08 (s, 9 H, C15-H).



[4-(*tert*-Butyldiphenylsilanyloxy)-6-methylpiperidine-2-yl]-methanol (mp4-125). TFA (8.5 mL) was added to a solution of **4.137** (683 mg, 1.41 mmol) in CH_2Cl_2 (8.5 mL) at 0 °C. The reaction was stirred at 0°C for 2 h, whereupon the volatiles were removed under reduced pressure. A saturated aqueous solution of $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2 (3 x 60 mL). The organic layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure to give 540 mg (99%) of the title compound as a pale yellow oil; ^{1}NMR (500 MHz, $CDCl_3$) δ 7.65-7.59 (comp, 4 H), 7.44-7.39 (comp, 2 H), 7.38-7.33 (comp, 4 H, Ar-H), 5.08 (br s, 1H), 3.93-3.88 (m, 1 H), 3.48-3.43 (m, 1 H), 3.89-3.36 (comp, 2 H), 3.21-3.16 (m, 1 H), 1.86 (td, *J* = 13.8, 3.9 Hz, 1 H), 1.55-1.52 (comp, 2 H), 1.49-1.43 (m, 1 H), 1.35 (d, *J* = 6.8 Hz, 1 H), 1.04 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.6, 133.5, 133.4, 130.0, 129.9, 127.8, 127.7, 65.5,

61.1, 50.9, 46.4, 38.4, 33.6, 26.9, 19.0. IR (neat) 3326, 2932, 2858, 1675, 1428, 1203, 1112, 702 cm^{-1}; (HRMS: CI; LRMS: ESI) *m/z* 384.2357 [$C_{23}H_{34}NO_2Si$ (M+1) requires 384.2359] 384 (base), 440, 583.

NMR Assignments. ^{1}NMR (500 MHz, $CDCl_3$) δ 7.65-7.59 (comp, 4 H, Ar-H), 7.44-7.39 (comp, 2 H, Ar-H), 7.38-7.33 (comp, 4 H, Ar-H), 5.08 (br s, 1H, NH), 3.93-3.88 (m, 1 H, C4-H), 3.48-3.43 (m, 1 H, C6-H), 3.89-3.36 (comp, 2 H, C7-H), 3.21-3.16 (m, 1 H, C2-H), 1.86 (td, *J* = 13.8, 3.9 Hz, 1 H, C3-H), 1.55-1.52 (comp, 2 H, C5-H), 1.49-1.43 (m, 1 H, C3-H), 1.35 (d, *J* = 6.8 Hz, 1 H, C8-H), 1.04 (s, 9 H, C14-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.6 (Ar-C), 133.5 (Ar-C), 133.4 (Ar-C), 130.0 (Ar-C), 129.9 (Ar-C), 127.8 (Ar-C), 127.7 (Ar-C), 65.5 (C4), 61.1 (C7), 50.9 (C6), 46.4 (C2), 38.4 (C3), 33.6 (C5), 26.9 (C14), 19.0 (C8).

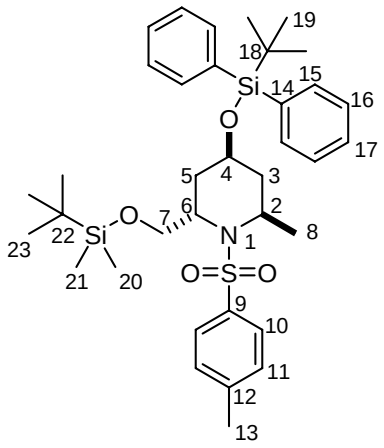


4.144

2-(*tert*-Butyldimethylsilanyloxymethyl)-4-(*tert*-butyldiphenylsilanyloxy)-6-methylpiperidine (4.144) (mp4-185). A solution of [4-(*tert*-Butyldiphenylsilanyloxy)-6-methylpiperidine-2-yl]-methanol (470 mg, 1.23 mmol), TBSCl (454 mg, 3.00 mmol) and imidazole (335 mg, 4.92 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature overnight. The reaction was poured into a separatory funnel containing brine (60 mL), and the aqueous mixture was extracted with CH_2Cl_2 (3 x 40 mL). The organic layer was dried (Na_2SO_4), the solvent was removed under reduced pressure, and the residue was

purified by flash chromatography eluting with 2% NH_4OH (20% aqueous solution) and 40% EtOAc in hexanes to give 457 mg (75 %) of **4.144** as a pale yellow oil; ^{1}NMR (500 MHz, $CDCl_3$) δ 7.66-7.63 (comp, 4 H), 7.42-7.38 (comp, 2 H), 7.37-7.32 (comp, 4 H), 3.73 (app hept, *J* = 4.3 Hz, 1 H), 3.35 (t, *J* = 9.3 Hz, 3 H), 3.12-3.04 (comp, 2 H), 2.78-2.72 (m, 1 H), 1.77-1.73 (m, 1 H), 1.61 (ddd, *J* = 13.0, 10.0, 5.2 Hz, 1 H), 1.49-1.44 (m, 1 H), 1.27 (dt, *J* = 12.4, 10.0 Hz, 1 H), 1.05 (d, *J* = 6.2 Hz, 1 H), 1.02 (s, 9 H), 0.82 (s, 9 H), -0.048 (s, 3H), -0.054 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.78, 135.76, 134.5, 134.4, 129.5, 127.5, 67.5, 62.8, 53.0, 44.2, 42.7, 35.1, 26.93, 25.86, 22.7, 19.1, 18.2, -5.4, -5.5; IR (neat) 3071, 2954, 2857, 1472, 1428, 1256, 1104, 836, 702 cm^{-1}; mass spectrum (ESI) *m/z* 498.3221 [$C_{29}H_{48}NO_2Si_2$ (M+1) requires 498.3218].

NMR Assignments. ^{1}NMR (500 MHz, $CDCl_3$) δ 7.66-7.63 (comp, 4 H, Ar-H), 7.42-7.38 (comp, 2 H, Ar-H), 7.37-7.32 (comp, 4 H, Ar-H), 3.73 (app hept, *J* = 4.3 Hz, 1 H, C4-H),), 3.35 (t, *J* = 9.3 Hz, 3 H, C7-H), 3.12-3.04 (comp, 2 H, C7-H, C6-H), 2.78-2.72 (m, 1 H, C2-H), 1.77-1.73 (m, 1 H, C3-H), 1.61 (ddd, *J* = 13.0, 10.0, 5.2 Hz, 1 H, C5-H), 1.49-1.44 (m, 1 H, C5-H), 1.27 (dt, *J* = 12.4, 10.0 Hz, 1 H, C3-H), 1.05 (d, *J* = 6.2 Hz, 1 H, C8-H), 1.02 (s, 9 H, C12-H), 0.82 (s, 9 H, C18-H), -0.048 (s, 3H, C10-H or C9-H), -0.054 (s, 3H, C10-H or C9-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.78 (Ar-C), 135.76 (Ar-C), 134.5 (Ar-C), 134.4 (Ar-C), 129.5 (Ar-C), 127.5 (Ar-C), 67.5 (C4), 62.8 (C7), 53.0 (C6), 44.2 (C2), 42.7 (C3), 35.1 (C5), 26.93 (C12), 25.86 (C18), 22.7 (C8), 19.1 (C17 or C11), 18.2 (C17 or C11), -5.4 (C10 or C9), -5.5 (C10 or C9).

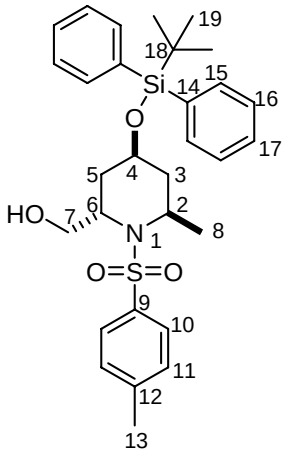


4.145

2-(*tert*-Butyldimethylsilanyloxymethyl)-4-(*tert*-butyldiphenylsilanyloxy)-6-methyl-1-(toluene-4-sulfonyl)-piperidine (4.145) (mp5-044). Toluenesulfonyl chloride (153 mg, 0.80 mmol) was added to a solution of **4.144** (200 mg, 0.40 mmol), Et_3N (0.17 mL, 1.21 mmol) and a catalytic amount of DMAP. The reaction was stirred at room temperature overnight, whereupon it was poured into EtOAc (50 mL) and washed with 0.5 M HCl (2 x 20 mL) and brine (20 mL). The organic layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with hexanes / EtOAc (5:1) to give 249 mg (95%) of **4.145** as a clear colorless oil; ^{1}NMR (500 MHz, $CDCl_3$) δ ^{1}NMR (500 MHz, $CDCl_3$) δ 7.24-7.70 (comp, 2 H), 7.63-7.60 (comp, 4 H), 7.42-7.37 (comp, 2 H), 7.35-7.32 (comp, 4 H), 7.22-7.19 (comp, 2 H), 4.31-4.26 (m, 1 H), 4.00-3.94 (m, 1 H), 3.65 (dd, *J* = 10.3, 6.1 Hz, 1 H), 3.53-3.45 (m, 1 H), 3.45 (dd, *J* = 10.3, 6.1 Hz, 1 H), 2.38 (s, 3 H), 1.92 (app dt, *J* = 13.4, 4.0, Hz, 1 H), 1.73 (ddd, *J* = 13.4, 9.5, 5.2, Hz, 1 H), 1.66 (app dt, *J* = 13.3, 3.5, Hz, 1 H), 1.57-1.52 (m, 1 H), 1.20 (d, *J* = 6.9, Hz, 1 H), 1.03 (s, 9 H), 0.80 (s, 9 H), -0.05 (s, 3 H), -0.06 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.6, 141.2, 135.75, 135.72, 134.2, 134.1, 129.7, 129.6, 129.3. 127.58, 127.56, 126.9, 66.5, 63.5, 55.5, 50.0, 41.6, 35.2, 26.9, 25.9, 24.1, 20.4, 19.1, 18.2, -5.47, -5.54; IR (neat) 2929, 2856, 1472, 1318, 1152, 1110,

1087 cm^{-1}; mass spectrum (CI) *m/z* 652.3312 [$C_{36}H_{54}NO_4Si_2S$(M+1) requires 652.3312], 396, 498, 574, 594, 652 (base).

NMR Assignments. ^{1}NMR (500 MHz, $CDCl_3$) δ 7.24-7.70 (comp, 2 H, Ar-H), 7.63-7.60 (comp, 4 H, Ar-H), 7.42-7.37 (comp, 2 H, Ar-H), 7.35-7.32 (comp, 4 H, Ar-H), 7.22-7.19 (comp, 2 H, Ar-H), 4.31-4.26 (m, 1 H, C6-H), 4.00-3.94 (m, 1 H, C4-H), 3.65 (dd, *J* = 10.3, 6.1 Hz, 1 H, C7-H), 3.53-3.45 (m, 1 H, C2-H), 3.45 (dd, *J* = 10.3, 6.1 Hz, 1 H, C7-H), 2.38 (s, 3 H, C13-H), 1.92 (app dt, *J* = 13.4, 4.0, Hz, 1 H, C5-H), 1.73 (ddd, *J* = 13.4, 9.5, 5.2, Hz, 1 H, C5-H), 1.66 (app dt, *J* = 13.3, 3.5, Hz, 1 H, C3-H), 1.57-1.52 (m, 1 H, C3-H), 1.20 (d, *J* = 6.9, Hz, 1 H, C8-H), 1.03 (s, 9 H, C19-H), 0.80 (s, 9 H, C23-H), -0.05 (s, 3 H, C20-H or C21-H), -0.06 (s, 3 H, C20-H or C21-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.6 (Ar-C), 141.2 (Ar-C), 135.75 (Ar-C), 135.72 (Ar-C), 134.2 (Ar-C), 134.1 (Ar-C), 129.7 (Ar-C), 129.6 (Ar-C), 129.3 (Ar-C), 127.58 (Ar-C), 127.56 (Ar-C), 126.9 (Ar-C), 66.5 (C4), 63.5 (C7), 55.5 (C6), 50.0 (C2), 41.6 (C3), 35.2 (C5), 26.9 (C13), 25.9 (C8), 24.1 (C19), 20.4 (C23), 19.1 (C18 or C22), 18.2 (C18 or C22), -5.47 (C20 or C21), -5.54 (C20 or C21).

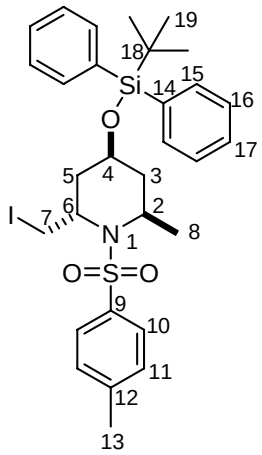


4.146

[4-(*tert*-butyldiphenylsilanyloxy)-6-methyl-1-(toluene-4-sulfonyl)-piperidine-2-yl]-methanol (4.146) (mp5-045). A solution of **4.145** (199 mg, 0.31 mmol) and camphorsulfonic acid (21 mg, 0.09 mmol) in MeOH (3 mL) and CH_2Cl_2 (3 mL) was stirred at 0 °C for 1 h, whereupon the ice bath was removed and the reaction stirred for an additional 30 min. Additional camphorsulfonic acid (70 mg, 0.31 mmol) was added, and the reaction was stirred at room temperature for 40 min, whereupon an aqueous saturated solution of $NaHCO_3$ (1 mL) was added. The mixture was poured into a saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with hexanes / EtOAc (2:1) to give 158 mg (96%) of **4.146** as a clear colorless oil; ^{1}NMR (500 MHz, $CDCl_3$) δ ^{1}NMR (500 MHz, $CDCl_3$) δ 7.70-7.67 (comp, 2 H), 7.59-7.56 (comp, 4 H), 7.43-7.39 (comp, 2 H), 7.36-7.32 (comp, 4 H), 7.23-7.21 (comp, 2 H), 4.20 (hept, *J* = 4.2, Hz, 1 H), 3.90-3.86 (m, 1 H), 3.84-3.75 (comp, 2 H, C2-H), 3.54 (ddd, *J* = 12.4, 8.0, 4.5 Hz, 1 H), 2.66 (dd, *J* = 8.0, 6.1 Hz, 1 H, OH), 2.37 (s, 3 H), 1.60 (app dt, *J* = 13.7, 4.2, Hz, 1 H), 1.54-1.46 (comp, 2 H), 1.43 (ddd, *J* = 13.8, 6.6, 4.1 Hz, 1 H), 1.37 (d, *J* = 6.9 Hz, 1 H), 1.02 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.2, 139.8, 135.7, 133.8, 133.7, 129.85, 129.80, 129.67, 127.68, 127.67, 126.9, 66.6, 63.2, 54.5, 50.6, 38.4, 34.9, 26.9, 21.5, 20.5, 19.0; IR (neat) 3530, 2931, 1428, 1316, 1150, 1111, 1086, 818, 703 cm^{-1}. mass spectrum (CI) *m/z* 538.2449 [$C_{30}H_{40}NO_4SSi$(M+1) requires 538.2447], 282, 352 (base), 384, 460, 538.

NMR Assignments. ^{1}NMR (500 MHz, $CDCl_3$) δ 7.70-7.67 (comp, 2 H, Ar-H), 7.59-7.56 (comp, 4 H, Ar-H), 7.43-7.39 (comp, 2 H, Ar-H), 7.36-7.32 (comp, 4 H, Ar-H), 7.23-7.21 (comp, 2 H, Ar-H), 4.20 (hept, *J* = 4.2, Hz, 1 H, C6-H), 3.90-3.86 (m, 1 H, C4-H), 3.84-3.75 (comp, 2 H, C2-H, C7-H), 3.54 (ddd, *J* = 12.4, 8.0, 4.5 Hz, 1 H, C7-H), 2.66 (dd, *J* = 8.0, 6.1 Hz, 1 H, OH), 2.37 (s, 3 H, C13-H), 1.60 (app dt, *J* = 13.7, 4.2, Hz,

1 H, C3-H), 1.54-1.46 (comp, 2 H, C3-H, C5-H), 1.43 (ddd, *J* = 13.8, 6.6, 4.1 Hz, 1 H, C5-H), 1.37 (d, *J* = 6.9 Hz, 1 H, C8-H), 1.02 (s, 9 H, C19-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.2 (Ar-C), 139.8 (Ar-C), 135.7 (Ar-C), 133.8 (Ar-C), 133.7 (Ar-C), 129.85 (Ar-C), 129.80 (Ar-C), 129.67 (Ar-C), 127.68 (Ar-C), 127.67 (Ar-C), 126.9 (Ar-C), 66.6 (C4), 63.2 (C7), 54.5 (C6), 50.6 (C2), 38.4 (C3), 34.9 (C5), 26.9 (C19), 21.5 (C13), 20.5 (C8), 19.0 (C18).

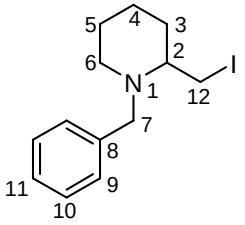


4.147

4-(*tert*-Butyldiphenylsilanyloxy)-2-iodomethyl-6-methyl-1-(toluene-4-sulfonyl)-piperidine (4.147) (mp5-045). Iodine (94 mg, 0.74 mmol) was added to a solution of **4.146** (66 mg, 0.12 mmol), PPh_3 (241 mg, 0.92 mmol), and imidazole (63 mg, 0.92 mmol) in CH_2Cl_2 (1.2 mL). The reaction was stirred at room temperature overnight, whereupon it was concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes / EtOAc (20:1 → 4:1) to give 55 mg (69%) of **4.147** as a clear colorless oil; ^{1}NMR (500 MHz, $CDCl_3$) δ 7.73-7.71 (comp, 2 H), 7.65-7.61 (comp, 4 H), 7.45-7.33 (comp, 6 H), 7.25-7.23 (comp, 2 H), 4.48-4.43 (m, 1H), 3.92 (hept, *J* = 4.4, Hz, 1 H), 3.45-3.40 (m, 1 H), 3.35 (dd, *J* = 9.9, 5.7, Hz, 1 H), 3.10 (app t, *J* = 9.9, Hz, 1 H), 2.39 (s, 3 H), 2.18 (dtd, *J* = 13.7, 4.4, 1.1 Hz, 1 H), 1.80 (ddd, *J* = 13.7,

9.7, 4.4 Hz, 1 H), 1.73-1.66 (m, 1 H), 1.58-1.53 (m, 1 H), 1.21 (d, *J* = 6.8 Hz, 1 H), 1.03 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.1, 140.4, 135.8, 135.7, 133.9, 133.7, 129.83, 129.76, 129.5, 127.8, 127.7, 127.1, 65.7, 55.8, 49.6, 41.3, 36.3, 26.9, 21.5, 20.5, 19.0, 6.2; IR (neat) 2929, 1427, 1317, 1151, 1112, 1088, 703 cm^{-1}; mass spectrum (CI) *m/z* 648.1467 [$C_{30}H_{39}NO_3SSiI$ (M+1) requires 648.1465], 352, 458 (base), 570, 648.

NMR Assignments. ^{1}NMR (500 MHz, $CDCl_3$) δ 7.73-7.71 (comp, 2 H, Ar-H), 7.65-7.61 (comp, 4 H, Ar-H), 7.45-7.33 (comp, 6 H, Ar-H), 7.25-7.23 (comp, 2 H, Ar-H), 4.48-4.43 (m, 1H, C6-H), 3.92 (hept, *J* = 4.4, Hz, 1 H, C4-H), 3.45-3.40 (m, 1 H, C2-H), 3.35 (dd, *J* = 9.9, 5.7, Hz, 1 H, C7-H), 3.10 (app t, *J* = 9.9, Hz, 1 H, C7-H), 2.39 (s, 3 H, C13-H), 2.18 (dtd, *J* = 13.7, 4.4, 1.1 Hz, 1 H, C5-H), 1.80 (ddd, *J* = 13.7, 9.7, 4.4 Hz, 1 H, C5-H), 1.73-1.66 (m, 1 H, C3-H), 1.58-1.53 (m, 1 H, C3-H), 1.21 (d, *J* = 6.8 Hz, 1 H, C8-H), 1.03 (s, 9 H, C19-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.1 (Ar-C), 140.4 (Ar-C), 135.8 (Ar-C), 135.7 (Ar-C), 133.9 (Ar-C), 133.7 (Ar-C), 129.83 (Ar-C), 129.76 (Ar-C), 129.5 (Ar-C), 127.8 (C11), 127.7 (Ar-C), 127.1 (Ar-10), 65.7 (C4), 55.8 (C6), 49.6 (C2), 41.3 (C3), 36.3 (C5), 26.9 (C19), 21.5 (C13), 20.5 (C8), 19.0 (C7), 6.2 (C18).

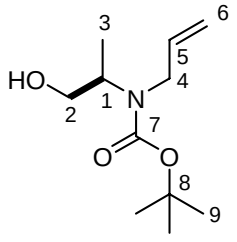


4.153

1-Benzy-2-iodomethylpiperidine (4.143), (mp4-277-1) Iodine (1.24 g, 9.74 mmol) was added to a solution of **4.152** (1.0 g, 4.87 mmol), PPh_3 (3.29 g, 12.2 mmol) and imidazole (830 mg, 12.2 mmol) in benzene (80 mL). The mixture was stirred at room temperature shielded from light for 20 min, whereupon a solution of $Na_2S_2O_3$ (10 g) in

saturated aqueous $NaHCO_3$ (100 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 60 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with hexanes / EtOAc (20:1 → 15:1) to give 589 mg (38%) of **4.153** as a yellow oil; ^{1}NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.5, Hz, 1 H), 7.31-7.28 (comp, 2 H), 7.24-7.21 (m, 1 H), 3.94 (d, *J* = 13.0 Hz, 1 H), 3.49 (dd, *J* = 10.5, 6.3 Hz, 1 H), 3.36 (dd, *J* = 10.5, 2.3 Hz, 1 H), 3.15 (d, *J* = 13.0, Hz, 1 H), 2.75-2.71 (m, 1 H), 2.11-2.02 (comp, 2 H), 1.74-1.63 (comp, 2 H), 1.50-1.36 (comp, 3 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9, 129.0, 128.2, 126.9, 59.8, 58.0, 50.8, 31.5, 25.3, 22.7, 13.4.

NMR Assignments. ^{1}NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.5, Hz, 1 H, C9-H), 7.31-7.28 (comp, 2 H, C10-H), 7.24-7.21 (m, 1 H, C11-H), 3.94 (d, *J* = 13.0 Hz, 1 H, C7-H), 3.49 (dd, *J* = 10.5, 6.3 Hz, 1 H, C12-H), 3.36 (dd, *J* = 10.5, 2.3 Hz, 1 H, C12-H), 3.15 (d, *J* = 13.0, Hz, 1 H, C7-H), 2.75-2.71 (m, 1 H, C6-H), 2.11-2.02 (comp, 2 H, C2-H, C6-H), 1.74-1.63 (comp, 2 H, C3-H, C4-H), 1.50-1.36 (comp, 3 H, C5-H, C3-H or C4-H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9 (C8), 129.0 (C9), 128.2 (C10), 126.9 (C11), 59.8 (C2), 58.0 (C7), 50.8 (C6), 31.5 (C3 or C4 or C5), 25.3 (C3 or C4 or C5), 22.7 (C3 or C4 or C5), 13.4 (C12).

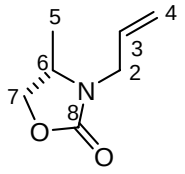


4.159

But-3-enyl-[1-methyl-2-(1-methyl-1-trimethylsilanylethoxy)ethyl]carbamic acid *tert*-butyl ester (4.159), (mp5-066, mp5-067, mp5-070). A solution of **4.156** (2.00 g, 13.3 mmol), TBSCl (3.00 g, 19.9 mmol) and imidazole (1.81 g, 26.6 mmol) in CH_2Cl_2 (30 mL) was stirred at room temperature for 3 h. MeOH (2 mL) was added and the reaction was stirred for 10 min, whereupon it was poured into EtOAc (150 mL) and washed with 0.5 M HCl (2 x 50 mL). The organic layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was dissolved in DMF (12 mL) and cooled to 0 °C. NaH (676 mg, 16.9 mmol) was added and the reaction was stirred at 0 °C for 10 min, whereupon allyl bromide (1.46 mL, 16.9 mmol) was added. The reaction was stirred over night, and NaH (484 mg, 12.1 mmol) and allyl bromide (1.05 mL, 12.1 mmol) were added. The reaction was stirred at room temperature for 3 h, whereupon it was poured into brine (80 mL) and extracted Et_2O (3 x 70 mL). The combined organic extracts were washed with brine (2 x 30 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with hexanes / EtOAc (20:1 → 15:1 → 10:1) to give 1.77 g (44%) of **4.158** as a clear colorless oil. TBAF (2.08 g, 7.95 mmol) was added to a solution of **4.158** (1.77 g, 5.3 mmol) in THF (50 mL) and the reaction was stirred at room temperature for 2 h. The reaction was poured into H_2O (150 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with hexanes / EtOAc (2:1) to give 1.01 g (89%) of **4.159** as a clear colorless oil; ^{1}NMR (500 MHz, $CDCl_3$) 5.87-5.57 (m, 1 H), 5.14-5.06 (comp, 2 H), 3.97 (br s, 1 H), 3.73 (br, s, 2 H), 3.57 (d, J = 5.6, Hz, 1 H), 2.49 (br s, 1 H), 1.43 (s, 9 H), 1.13 (d, J = 6.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 135.6, 116.0, 80.0, 65.6, 54.2, 47.2, 28.4, 14.7; IR (neat)

3435, 2977, 1672, 1454, 1407, 1366 cm^{-1}. mass spectrum (CI) *m/z* 216.1609 [$C_{11}H_{22}NO_3$ (M+1) requires 216.1600], 184, 216 (base).

NMR Assignments. ^{1}NMR (500 MHz, $CDCl_3$) 5.87-5.57 (m, 1 H, C5-H), 5.14-5.06 (comp, 2 H, C6-H), 3.97 (br s, 1 H, C1-H), 3.73 (br, s, 2 H, C4-H), 3.57 (d, *J* = 5.6, Hz, 1 H, C2-H), 2.49 (br s, 1 H, OH), 1.43 (s, 9 H, C9-H), 1.13 (d, *J* = 6.1 Hz, 3 H, C3-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5 (C7), 135.6 (C5), 116.0 (C6), 80.0 (C8), 65.6 (C2), 54.2 (C1), 47.2 (C4), 28.4 (C9), 14.7 (C3).

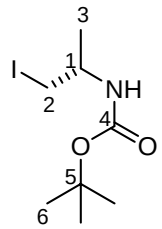


4.161

3-But-3-enyl-4-methyloxazolidine-2-one (4.161), mp5-071). Iodine (88 mg, 0.67 mmol) was added to a solution of **4.159** (100 mg, 0.46 mmol), PPh_3 (250 mg, 0.93 mmol) and imidazole (63 mg, 0.93 mmol) in CH_2Cl_2 (4.6 mL). The reaction was stirred at room temperature overnight, whereupon it was concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes / EtOAc (1:1) to give 48 mg (73%) of **4.161** as a clear colorless oil; ^{1}NMR (500 MHz, $CDCl_3$) 5.77-5.68 (m, 1 H), 5.23-5.16 (comp, 2 H), 4.36 (app t, *J* = 7.8, Hz, 1 H), 4.09-4.04 (m, 1 H), 3.87-3.78 (m, 1 H), 3.78 (app t, *J* = 7.8 Hz, 1 H), 3.61-3.56 (m, 1 H), 1.21 (d, *J* = 5.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.9, 132.2, 118.4, 68.9, 50.6, 44.4, 18.0; IR (neat) 2975, 1747, 1412, 1254 cm^{-1}; mass spectrum (CI) *m/z* 142.0871 [$C_7H_{12}NO_2$ (M+1) requires 142.0868] 116, 142 (base).

NMR Assignments. ^{1}NMR (500 MHz, $CDCl_3$) 5.77-5.68 (m, 1 H, C3-H), 5.23-5.16 (comp, 2 H, C4-H), 4.36 (app t, *J* = 7.8, Hz, 1 H, C7-H), 4.09-4.04 (m, 1 H, C2-H),

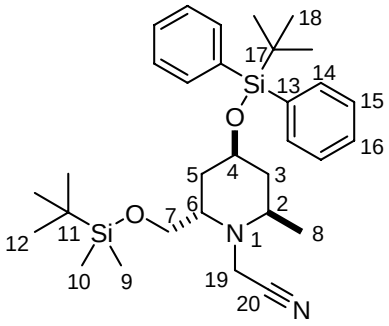
3.87-3.78 (m, 1 H, C6-H), 3.78 (app t, J = 7.8 Hz, 1 H, C7-H), 3.61-3.56 (m, 1 H, C2-H), 1.21 (d, J = 5.9 Hz, 3 H, C5-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.9 (C8), 132.2 (C3), 118.4 (C4), 68.9 (C7), 50.6 (C6), 44.4 (C2), 18.0 (C5).



4.163

(2-Iodo-1-methylethyl)carbamic acid tert-butyl ester (4.163), (mp5-132). Iodine (728 mg, 5.74 mmol) was added to a solution of **4.131** (500 mg, 2.87 mmol), PPh_3 (1.93 g, 7.17 mmol) and imidazole (488 mg, 7.16 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The reaction was stirred at 0 °C for 45 min, whereupon the cold bath was removed and the reaction was stirred at room temperature for 7 h. The reaction was poured into H_2O (50 mL) and the aqueous mixture was extracted with CH_2Cl_2 (2 x 40 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with hexanes / EtOAc (7:1) to give 386 mg (47%) of **4.163** as a brown oil; ^{1}NMR (500 MHz, $CDCl_3$) 4.62-4.59 (m, 1 H), 3.53-3.45 (m, 1 H), 3.41-3.32 (m, 1 H), 3.26 (dd, J = 9.9, 3.8 Hz, 1 H), 1.41 (s, 9 H), 1.16 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 79.6, 45.9, 28.3, 21.1, 15.

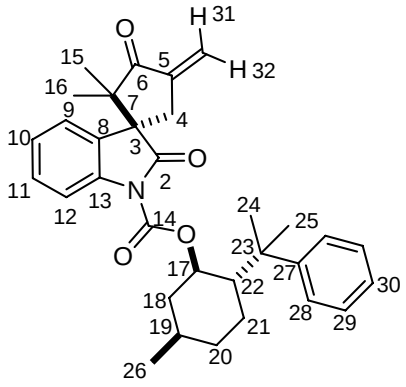
NMR Assignments. ^{1}NMR (500 MHz, $CDCl_3$) 4.62-4.59 (m, 1 H, NH), 3.53-3.45 (m, 1 H, C1-H), 3.41-3.32 (m, 1 H, C2-H), 3.26 (dd, J = 9.9, 3.8 Hz, 1 H, C2-H), 1.41 (s, 9 H, C6-H), 1.16 (d, J = 6.6 Hz, 3 H, C3-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8 (C4), 79.6 (C3), 45.9 (C1), 28.3 (C6), 21.1 (C3), 15 (C2).



4.172

[2-(*tert*-Butyldimethylsilanyloxymethyl)-4-(*tert*-butyldiphenylsilanyloxy)-6-methylpiperidine-1-yl]-acetonitrile (4.172) (mp4-193). Iodoacetonitrile (81 μL, 1.60 mmol) was added to a solution of **4.144** (250 mg, 0.50 mmol) and *i*-Pr_2EtN (0.35 mL, 2.00 mmol) in THF (5 mL). The mixture was stirred at room temperature overnight, whereupon it was diluted with EtOAc (75 mL). The solution was washed with a saturated aqueous solution of $NaHCO_3$ (30 mL) and brine (30 mL). The organic layer was dried (Na_2SO_4), the solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with hexanes / EtOAc (6:1) to give 250 mg (93%) of **4.172** as a clear yellow oil; ^{1}NMR (500 MHz, $CDCl_3$) δ 7.65-7.62 (comp, 4 H), 7.43-7.33 (comp, 6 H), 3.79 (d, *J* = 17.4, Hz, 1 H), 3.78-3.73 (m, 1 H), 3.68 (dd, *J* = 10.9, 6.5 Hz, 1 H), 3.51 (d, *J* = 17.4 Hz, 1 H), 3.15 (dd, *J* = 10.9, 4.4, Hz, 1 H), 3.07-3.02 (m, 1 H), 2.89-2.82 (m, 1 H), 1.80-1.75 (m, 1 H), 1.69-1.64 (m, 1 H), 1.58 (ddd, *J* = 12.8, 9.9, 4.9 Hz, 1 H), 1.40 (dt, *J* = 12.7, 9.7 Hz, 1 H), 1.14 (d, *J* = 6.3 Hz, 3 H), 1.04 (s, 9 H), 0.82 (s, 9 H), -0.05 (s, 3 H), -0.06 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.8, 135.7, 134.3, 134.2, 129.6, 127.6, 117.6, 66.5, 61.9, 60.8, 49.5, 42.5, 40.4, 37.4, 26.9, 25.9, 19.8, 19.1, 18.1, -5.55, -5.62; IR (neat) 2938, 2856, 1472, 1427, 1256, 1105, 837, 702 cm^{-1}; mass spectrum (ESI) *m/z* 537.3334 [$C_{31}H_{49}N_2O_2Si_2$ (M+1) requires 537.3327], 498, 537 (base), 559.

NMR Assignments. ^{1}NMR (500 MHz, $CDCl_3$) δ 7.65-7.62 (comp, 4 H, Ar-H), 7.43-7.33 (comp, 6 H, Ar-H), 3.79 (d, *J* = 17.4, Hz, 1 H, C19-H), 3.78-3.73 (m, 1 H, C4-H), 3.68 (dd, *J* = 10.9, 6.5 Hz, 1 H, C7-H), 3.51 (d, *J* = 17.4 Hz, 1 H, C19-H), 3.15 (dd, *J* = 10.9, 4.4, Hz, 1 H, C7-H), 3.07-3.02 (m, 1 H, C6-H), 2.89-2.82 (m, 1 H, C2-H), 1.80-1.75 (m, 1 H, C3-H), 1.69-1.64 (m, 1 H, C5-H), 1.58 (ddd, *J* = 12.8, 9.9, 4.9 Hz, 1 H, C5-H), 1.40 (dt, *J* = 12.7, 9.7 Hz, 1 H, C3-H), 1.14 (d, *J* = 6.3 Hz, 3 H, C8-H), 1.04 (s, 9 H, C12-H), 0.82 (s, 9 H, C18-H), -0.05 (s, 3 H, C9-H or C10-H), -0.06 (s, 3 H, C9-H or C10-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.8 (Ar-C), 135.7 (Ar-C), 134.3 (Ar-C), 134.2 (Ar-C), 129.6 (Ar-C), 127.6 (Ar-C), 117.6 (C-20), 66.5 (C4), 61.9 (C7), 60.8 (C6), 49.5 (C2), 42.5 (C3), 40.4 (C9), 37.4 (C5), 26.9 (C12), 25.9 (C18), 19.8 (C8), 19.1 (C17 or C11), 18.1 (C17 or C11), -5.55 (C9 or C10), -5.62 (C9 or C10).



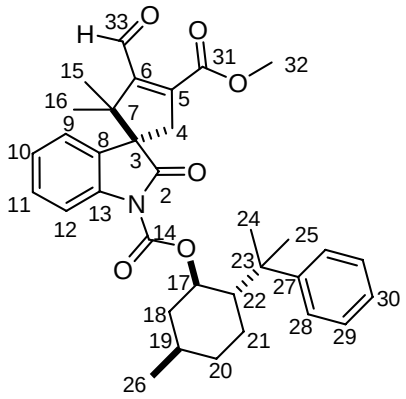
4.175

Ketone 4.175 (mp4-192). LDA (0.25 mL, 0.4 M, 0.10 mmol) was added to a solution of **4.77** (40 mg, 0.08 mmol) in THF (1 mL) at −78 °C. The reaction was stirred at −78 °C for 30 min, whereupon a solution of Eschenmoser salt (46 mg, 0.25 mmol) in THF (0.5 mL) was added. The cold bath was removed and the reaction was stirred for 1 h, whereupon a saturated aqueous solution of NH_4Cl (1 mL) was added. The mixture was poured into H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic

layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was dissolved in MeOH (0.2 mL), and MeI (60 μL, 1.0 mmol) was added. The reaction was stirred at room temperature overnight, whereupon it was poured into H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with hexanes / EtOAc (3:1) to give 7 mg (17%) of **4.77** and 24 mg (58%) of **4.175** as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.2 Hz, 1 H), 7.32 (td, *J* = 8.5, 1.4 Hz, 1 H), 7.24 (d, *J* = 7.4 Hz, 2 H), 7.16-7.09 (comp, 2 H), 7.02 (t, *J* = 7.4 Hz, 2 H), 6.85 (t, *J* = 7.4 Hz), 6.25 (t, *J* = 2.3 Hz, 1 H), 5.50 (t, *J* = 2.4 Hz, 1 H), 5.08 (td, *J* = 10.6, 4.8 Hz, 1 H), 3.00 (dt, *J* = 17.4, 2.4 Hz, 1 H), 2.89 (dt, *J* = 17.4, 2.4 Hz, 1 H), 1.96-1.90 (m, 1 H), 1.96-1.90 (m, 1 H), 1.77-1.69 (m, 1 H), 1.66-1.60 (m, 1 H), 1.51-1.41 (m, 1 H), 1.34 (s, 3H), 1.32-1.24 (m, 1 H), 1.24 (s, 3 H), 1.18-1.07 (m, 1 H), 0.99 (s, 3 H), 0.99 (s, 3 H), 0.93-0.83 (m, 1 H), 0.87 (d, *J* = 6.5 Hz, 3 H); mass spectrum (CI) *m/z* 215 (base), 286, 499 (M+1), 528, 488.

NMR Assignments. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.2 Hz, 1 H, C9-H or C12-H), 7.32 (td, *J* = 8.5, 1.4 Hz, 1 H, C10-H or C11-H), 7.24 (d, *J* = 7.4 Hz, 2 H, C28-H), 7.16-7.09 (comp, 2 H, C10-H or C11-H, C9-H or C12-H), 7.02 (t, *J* = 7.4 Hz, 2 H, C29-H), 6.85 (t, *J* = 7.4 Hz, C30-H), 6.25 (t, *J* = 2.3 Hz, 1 H, C31-H or C32-H), 5.50 (t, *J* = 2.4 Hz, 1 H, C31-H or C32-H), 5.08 (td, *J* = 10.6, 4.8 Hz, 1 H, C17-H), 3.00 (dt, *J* = 17.4, 2.4 Hz, 1 H, C4-H), 2.89 (dt, *J* = 17.4, 2.4 Hz, 1 H, C4-H), 1.96-1.90 (m, 1 H, C22-H), 1.96-1.90 (m, 1 H, C18-H), 1.77-1.69 (m, 1 H, C21-H), 1.66-1.60 (m, 1 H, C20-H), 1.51-1.41 (m, 1 H, C19-H), 1.34 (s, 3H, C15-H or C16-H), 1.32-1.24 (m, 1 H, C18-H), 1.24 (s, 3 H, C15-H or C-16), 1.18-1.07 (m, 1 H, C21-H), 0.99 (s, 3 H, C24-H or

C25-H), 0.99 (s, 3 H, C24-H or C25-H), 0.93-0.83 (m, 1 H, C20-H), 0.87 (d, J = 6.5 Hz, 3 H, C26-H).



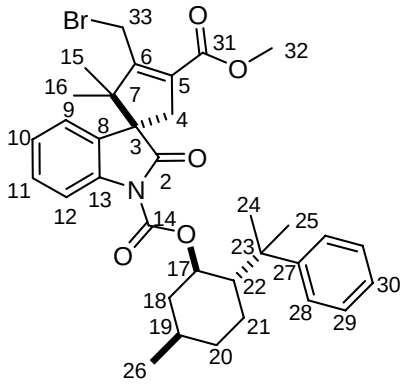
4.179

Aldehyde 4.179 (mp4-299, mp4-302). $Pd_2(dba)_3$ (99 mg, 0.11 mmol) was added to a solution of **4.80** (364 mg, 0.54 mmol) and Ph_3As (131 mg, 0.43) in degassed DMF/THF 2:1 (11 mL), and the mixture was stirred at room temperature for 15 min. Tributylvinyltin (0.47 mL, 1.61 mmol) was added, and the reaction was stirred at room temperature for 6.5 h, whereupon it was poured into a separatory funnel containing brine (40 mL). The mixture was extracted with Et_2O (3 x 40 mL), and the combined organic layers were dried (Na_2SO_4), the solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with hexanes / EtOAc (4:1) to give **4.178** as a clear colorless oil. The purified alkene was dissolved in dioxane (4 mL). 2,6-lutidine (0.25 mL, 2.15 mmol), H_2O (1.3 mL), and a 2.5% wt solution of OsO_4 in *t*-butyl alcohol (0. 27 mL, 0.02 mmol) was added followed by $NaIO_4$ (920 mg, 4.30 mmol). The reaction was stirred at room temperature for 2 h, whereupon it was poured into a separatory funnel containing H_2O (40 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were dried (Na_2SO_4), the solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with hexanes /

EtOAc (5:1) to give 190 mg (63%, 2 steps) of **4.179** as a dark grey oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.45 (s, 1 H), 7.77 (d, *J* = 8.2 Hz, 1 H), 7.33-7.29 (m, 1 H), 7.25-7.20 (comp, 3 H), 7.13 (td, *J* = 7.6, 1.1 Hz, 1 H), 7.03-7.00 (comp, 2 H), 6.89-6.85 (m, 1 H), 5.08 (td, *J* = 10.9, 4.8 Hz, 1 H), 3.87 (s, 3 H), 3.18 (d, *J* = 18.5 Hz, 1 H), 3.01 (d, *J* = 18.5 Hz, 1 H), 2.18-2.13 (m, 1 H), 1.95-1.91 (m, 1 H), 1.72 (dq, *J* = 13.5, 3.5 Hz, 1 H), 1.65-1.60 (m, 1 H), 1.50-1.43 (m, 1 H), 1.35 (s, 3H), 1.52 (s, 3 H), 1.22-1.18 (m, 1 H), 1.14 (s, 3H), 1.11 (s, 3H), 1.17-1.08 (m, 1 H), 0.90-0.83 (m, 1 H), 0.87 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz) δ 190.7, 175.6, 163.9, 153.4, 151.0, 149.8, 143.4, 139.8, 128.8, 127.8, 127.2, 125.4, 124.9, 124.4, 124.0, 115.0, 59.1, 54.7, 52.5, 50.6, 41.8, 41.1, 39.8, 34.3, 31.5, 27.8, 26.6, 25.2, 24.4, 21.7, 21.2; IR (neat) 2955, 1769, 1722, 1677, 1464, 1242 cm^{-1}; mass spectrum (CI) *m/z* 558.2855 [$C_{34}H_{40}NO_6$ (M+1) requires 558.2855], 260, (base), 371, 557, 558.

NMR Assignments. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.45 (s, 1H), 7.77 (d, *J* = 8.2 Hz, 1 H, C9-H or C12-H), 7.33-7.29 (m, 1 H, C10-H or C11-H), 7.25-7.20 (comp, 3 H, C9-H or C12-H, C28-H), 7.13 (td, *J* = 7.6, 1.1 Hz, 1 H, C10-H or C11-H), 7.03-7.00 (comp, 2 H, C29-H), 6.89-6.85 (m, 1 H, C30-H), 5.08 (td, *J* = 10.9, 4.8 Hz, 1 H, C17-H), 3.87 (s, 3 H, C32-H), 3.18 (d, *J* = 18.5 Hz, 1 H, C4-H), 3.01 (d, *J* = 18.5 Hz, 1 H, C4-H), 2.18-2.13 (m, 1 H, C22-H), 1.95-1.91 (m, 1 H, C18-H), 1.72 (dq, *J* = 13.5, 3.5 Hz, 1 H, C21-H), 1.65-1.60 (m, 1 H, C22-H), 1.50-1.43 (m, 1 H, C19-H), 1.35 (s, 3H, C24-H or C25-H), 1.52 (s, 3 H, C15-H or C-16), 1.22-1.18 (m, 1 H, C18-H), 1.14 (s, 3H, C24-H or C25-H), 1.11 (s, 3H, C15-H or C16-H), 1.17-1.08 (m, 1 H, C21-H), 0.90-0.83 (m, 1 H, C21-H), 0.87 (d, *J* = 6.5 Hz, 3 H, C26-H); ^{13}C NMR (125 MHz) δ 190.7 (C33), 175.6 (C2), 163.9 (C31), 153.4 (C6), 151.0 (C14), 149.8 (C27), 143.4 (C13), 139.8 (C5), 128.8 (C10 or C11), 127.8 (C29), 127.2 (C8), 125.4 (C28), 124.9 (C30), 124.4 (C9 or C12), 124.0 (C10 or C11), 115.0 (C9 or C12), 59.1 (C3), 54.7 (C7), 52.5 (C32), 50.6 (C22),

41.8 (C18), 41.1 (C4), 39.8 (C23), 34.3 (C20), 31.5 (C19), 27.8 (C15 or C16), 26.6 (C21), 25.2 (C24 or C25), 24.4 (C15 or C16), 21.7 (C26), 21.2 (C24 or C25).

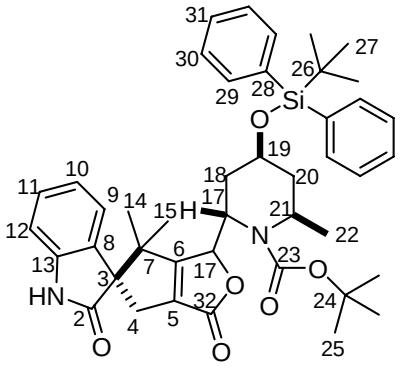


4.181

Allyl bromide 4.181 (mp5-029, mp5-033). A solution of $NaBH_4$ (0.2 M, 1.36 mL, 0.27 mmol) in EtOH was added to a solution of **4.179** (117 mg, 0.21 mmol) in CH_2Cl_2 (2.8 mL) at −78 °C. The reaction was stirred at −78 °C for 2 h, whereupon a saturated aqueous solution of NH_4Cl (2 mL) was added and the cold bath removed. Stirring was continued for 15 min, and the reaction was poured into a separatory funnel containing water (50 mL). The aqueous mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure The residue was purified by flash chromatography eluting with hexanes / EtOAc (2:1) to give 95 mg (81%) of **4.180** as a clear colorless oil. CBr_4 (35 mg, 0.11 mmol), was added to a solution of **4.180** (45 mg, 0.08 mmol), and PPh_3 (28 mg, 0.11 mmol) in CH_2Cl_2 (0.8 mL). The reaction was stirred at room temperature for 30 min, whereupon it was concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes / EtOAc (5:1) to give 43 mg (73%) of **4.181** as a clear colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 7.8 Hz, 1 H), 7.29-7.23 (comp, 4 H), 7.10 (d, J = 7.5 Hz, 1 H), 7.03-7.00 (comp, 2 H), 6.87-6.84 (m, 1 H), 5.01

(td, J = 10.9, 4.7 Hz, 1 H), 4.75 (d, J = 9.5 Hz, 1 H), 4.02 (d, J = 9.5 Hz, 1 H), 3.82 (s, 3 H), 3.18 (d, J = 17.0 Hz, 1 H), 2.84 (d, J = 17.0 Hz, 1 H), 2.20-2.14 (m, 1 H), 1.98-1.94 (m, 1 H), 1.73 (dq, J = 13.6, 3.4 Hz, 1 H), 1.66-1.61 (m, 1 H), 1.52-1.45 (m, 1 H), 1.35 (s, 3H), 1.29-1.22 (m, 1 H), 1.25 (s, 3 H), 1.19-1.10 (m, 1 H), 1.13 (s, 3 H), 0.99 (s, 3H), 0.93-0.86 (m, 1 H), 0.88 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz) δ 175.0, 164.5, 156.0, 150.9, 149.9, 139.0, 129.7, 129.5, 128.5, 127.8, 125.4, 125.0, 124.1, 123.8, 114.9, 58.8, 55.6, 51.8, 50.6, 41.8, 40.9, 39.8, 34.3, 31.5, 27.8, 26.6, 25.1, 23.3, 22.8, 22.1, 21.2; IR (neat) 2954, 1767, 1716, 1479, 1464, 1261 cm^{-1}; mass spectrum (CI) *m/z* 622.2157 [$C_{34}H_{41}NO_5Br$ (M+1) requires 622.2168], 251 (base), 364, 408, 542, 622 ,624.

NMR Assignments. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 7.8 Hz, 1 H, C9-H or C12-H), 7.29-7.23 (comp, 4 H, C10-H or C11-H, C9-H or C12-H, C28), 7.10 (d, J = 7.5 Hz, 1 H, C10-H or C11-H), 7.03-7.00 (comp, 2 H, C29-H), 6.87-6.84 (m, 1 H, C30-H), 5.01 (td, J = 10.9, 4.7 Hz, 1 H, C17-H), 4.75 (d, J = 9.5 Hz, 1 H, C33-H), 4.02 (d, J = 9.5 Hz, 1 H, C4-H), 3.82 (s, 3 H, C32-H), 3.18 (d, J = 17.0 Hz, 1 H, C4-H), 2.84 (d, J = 17.0 Hz, 1 H, C4-H), 2.20-2.14 (m, 1 H, C22-H), 1.98-1.94 (m, 1 H, C18-H), 1.73 (dq, J = 13.6, 3.4 Hz, 1 H, C21-H), 1.66-1.61 (m, 1 H, C20-H), 1.52-1.45 (m, 1 H, C19-H), 1.35 (s, 3H, C24-H or C25-H), 1.29-1.22 (m, 1 H, C18-H), 1.25 (s, 3 H, C15-H or C-16), 1.19-1.10 (m, 1 H, C21-H), 1.13 (s, 3 H, C24-H or C25-H), 0.99 (s, 3H, C15-H or C16-H), 0.93-0.86 (m, 1 H, C20-H), 0.88 (d, J = 6.5 Hz, 3 H, C26-H); ^{13}C NMR (125 MHz) δ 175.0 (C2), 164.5 (C31), 156.0 (C6), 150.9 (C14), 149.9 (C27), 139.0 (C13), 129.7 (C5), 129.5 (C8), 128.5 (C10 or C11), 127.8 (C29), 125.4 (C28), 125.0 (C30), 124.1 (C10 or C11), 123.8 (C9 or C12), 114.9 (C9 or C12), 58.8 (C3), 55.6 (C7), 51.8 (C32), 50.6 (C22), 41.8 (C18), 40.9 (C4), 39.8 (C23), 34.3 (C20), 31.5 (C19), 27.8 (C15 or C16), 26.6 (C21), 25.1 (C24 or C25), 23.3 (C15 or C16), 22.8 (C24 or C25), 22.1 (C33), 21.2 (C26).

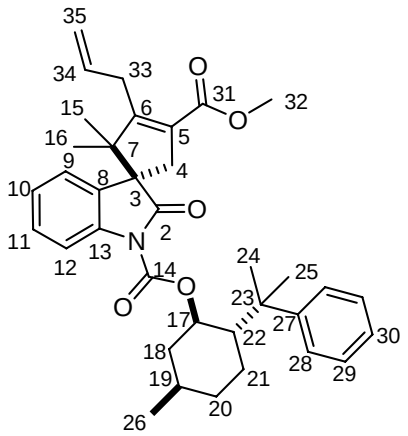


4.185

Oxindole 4.185 (mp4-285, mp4-298). A solution of *sec*-BuLi (1.66 M, 34 μL, 0.06 mmol) was added to a solution of **4.135** (31 mg, 0.07 mmol) in Et_2O (0.5 mL) and TMEDA (9 μL. 0.06 mmol) at −78 °C, and the reaction was stirred for 2.75 h. This solution was then added via cannula to a solution of **4.179** (29 mg, 0.05 mmol) in Et_2O (0.5 mL) at −100 °C, and the reaction was stirred at −100 °C for 30 min, whereupon the cold bath was replaced with a −78 °C bath. The reaction was stirred at this temperature for 1 h, whereupon the cold bath was removed. After stirring for 10 min, a saturated aqueous solution of NH_4Cl (1 mL) was added. The slurry was poured into H_2O (10 mL), and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with hexanes / EtOAc (3:1) to give 7 mg (24%) of recovered **4.179** and 7 mg (12%) of **4.184** as a clear colorless oil. K_2CO_3 (10 mg, 0.076 mmol) was added to a solution of **4.184** (7 mg, 0.006 mmol) in MeOH (0.5 mL), and the reaction was stirred at room temperature for 20 min, whereupon a saturated aqueous solution of NH_4Cl (1 mL) and H_2O (1 mL) were added. The aqueous mixture was extracted with EtOAc (2 x 4 mL), and the combined organic layers were dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified

by flash chromatography eluting with hexanes / EtOAc (3:1) to give 3 mg (70%) of **4.185** as a clear colorless oil.^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67-7.64 (comp, 2 H), 7.61-7.58 (comp, 2 H), 7.45-7.35 (comp, 6 H), 7.27-7.24 (m, 1 H), 7.08 (d, *J* = 7.6, 1 H), 7.01 (td, *J* = 7.6, 1.0 Hz,1 H), 6.83 (d, *J* = 7.6 Hz,1 H), 5.28-5.26 (m, 1 H), 4.22 (q, *J* = 6.9 Hz 1 H), 4.18-4.16 (m, 1 H), 4.08-4.02 (m, 1 H), 2.80 (dd, *J* = 16.1, 2.6 Hz, 1 H), 2.62 (dd, *J* = 16.1, 2.6 Hz, 1 H), 2.46-2.40 (m, 1 H), 1.81-1.75 (comp, 2 H, C18-H), 1.44 (s, 9H), 1.42-1.35 (comp, 3 H), 1.20 (s, 3 H), 1.06 (s, 9 H), 0.91 (s, 3H). ; IR (neat) 3252, 2971, 2922, 1766, 1709, 1679, 1471, 1391, 1370, 1106, 1058 cm^{-1}; mass spectrum (CI) *m/z* 721.3671 [$C_{43}H_{53}N_2O_6Si$ (M+1) requires 721.3673], 575, 619, 720 (base, M-1), 722.

NMR Assignments. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67-7.64 (comp, 2 H, Ar-H), 7.61-7.58 (comp, 2 H, Ar-H), 7.45-7.35 (comp, 6 H, Ar-H), 7.27-7.24 (m, 1 H, C10-H or C11-H), 7.08 (d, *J* = 7.6, 1 H, C9-H or C12-H), 7.01 (td, *J* = 7.6, 1.0 Hz,1 H, C10-H or C11-H), 6.83 (d, *J* = 7.6 Hz,1 H, C9-H or C12-H), 5.28-5.26 (m, 1 H, C16-H), 4.22 (q, *J* = 6.9 Hz 1 H, C19-H), 4.18-4.16 (m, 1 H, C17-H), 4.08-4.02 (m, 1 H, C21-H), 2.80 (dd, *J* = 16.1, 2.6 Hz, 1 H, C4-H), 2.62 (dd, *J* = 16.1, 2.6 Hz, 1 H, C4-H), 2.46-2.40 (m, 1 H, C18-H), 1.81-1.75 (comp, 2 H, C18-H, C20-H), 1.44 (s, 9H, C25-H), 1.42-1.35 (comp, 3 H, C22-H, C20-H), 1.20 (s, 3 H, C14-H or C-15), 1.06 (s, 9 H, C27-H), 0.91 (s, 3H, C14-H or C15-H).

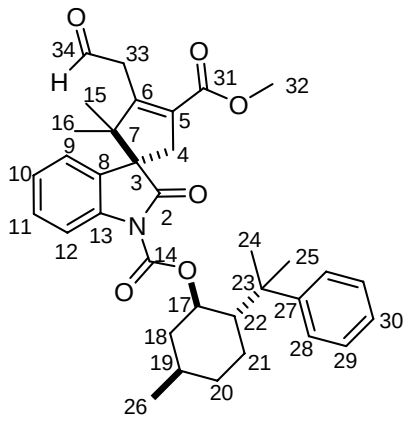


4.200

Enoate 4.200 (mp5-098). $Pd_2(dba)_3$ (25 mg, 0.03 mmol) was added to a solution of **4.80** (88 mg, 0.14 mmol) and Ph_3As (33 mg, 0.11) in degassed DMF/THF 2:1 (2.8 mL), and the mixture was stirred at room temperature for 15 min. Allyltributyltin (0.11 mL, 0.39 mmol) was added, and the reaction was stirred at 50 °C overnight, whereupon it was allowed to cool to room temperature and poured into a separatory funnel containing brine (20 mL). The mixture was extracted with Et_2O (3 x 20 mL), and the combined organic layers were dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with hexanes / EtOAc (10:1) to give 49 mg (64%) of **4.200** as a clear colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.2 Hz, 1 H), 7.27-7.23 (comp, 3 H), 7.19 (dd, *J* = 7.5, 1.0 Hz,1 H), 7.07 (td, *J* = 7.5, 1.0 Hz, 1 H), 7.02 (t, *J* = 7.4 Hz, 2 H), 6.86 (t, *J* = 7.4 Hz, 1 H), 5.84 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1 H), 5.13 (dd, *J* = 16.9, 1.6 Hz, 1 H), 5.09 (td, *J* = 10.7, 4.5 Hz, 1 H), 5.02 (dd, *J* = 10.1, 1.6 Hz, 1 H), 3.76 (s, 3 H), 3.37 (d, *J* = 13.8, 6.8 Hz, 1 H), 3.18 (dd, *J* = 13.8, 6.8 Hz, 1 H), 3.12 (d, *J* = 16.1 Hz, 1 H), 2.82 (d, *J* = 16.1 Hz, 1 H), 2.19-2.14 (m, 1 H), 1.99-1.93 (m, 1 H), 1.72 (dq, *J* = 13.6, 3.3 Hz, 1 H), 1.52-1.43 (m, 1 H), 1.35 (s, 3H), 1.30-1.20 (m, 1 H), 1.26 (s, 3 H), 1.17-1.09 (m, 1 H), 1.05 (s, 3 H), 0.93-

0.85 (m, 1 H), 0.88 (d, J = 6.5 Hz, 3 H), 0.83 (s, 3H); ^{13}C NMR (125 MHz) δ 175.5, 165.5, 160.5, 150.9, 149.9, 139.1, 135.2, 130.1, 128.2, 127.8, 125.39, 125.36, 125.0, 123.9, 123.7, 116.5, 114.8, 77.1, 58.8, 56.4, 51.3, 50.6, 41.8, 40.7, 39.8, 34.3, 31.7, 31.4, 27.6, 26.6, 25.3, 23.4, 22.4, 21.7; IR (neat) 2957, 1769, 1768, 1465, 1358, 1292, 1250 cm^{-1}; mass spectrum (CI) *m/z* 570.3216 [$C_{36}H_{44}NO_5$ (M+1) requires 570.3219], 538, 554, 570 (base), 598.

NMR Assignments. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J = 8.2 Hz, 1 H, C9-H or C12-H), 7.27-7.23 (comp, 3 H, C10-H or C11-H, C28-H), 7.19 (dd, J = 7.5, 1.0 Hz,1 H, C9-H or C12-H), 7.07 (td, J = 7.5, 1.0 Hz, 1 H, C10-H or C11-H), 7.02 (t, J = 7.4 Hz, 2 H, C29-H), 6.86 (t, J = 7.4 Hz, 1 H, C30-H), 5.84 (ddt, J = 16.9, 10.1, 6.6 Hz, 1 H, C34-H), 5.13 (dd, J = 16.9, 1.6 Hz, 1 H, C35-H), 5.09 (td, J = 10.7, 4.5 Hz, 1 H, C17-H), 5.02 (dd, J = 10.1, 1.6 Hz, 1 H, C35-H), 3.76 (s, 3 H, C32-H), 3.37 (d, J = 13.8, 6.8 Hz, 1 H, C33-H), 3.18 (dd, J = 13.8, 6.8 Hz, 1 H, C33-H), 3.12 (d, J = 16.1 Hz, 1 H, C4-H), 2.82 (d, J = 16.1 Hz, 1 H, C4-H), 2.19-2.14 (m, 1 H, C22-H), 1.99-1.93 (m, 1 H, C18-H), 1.72 (dq, J = 13.6, 3.3 Hz, 1 H, C21-H), 1.52-1.43 (m, 1 H, C19-H), 1.35 (s, 3H, C24-H or C25-H), 1.30-1.20 (m, 1 H, C18-H), 1.26 (s, 3 H, C15-H or C-16), 1.17-1.09 (m, 1 H, C21-H), 1.05 (s, 3 H, C24-H or C25-H), 0.93-0.85 (m, 1 H, C20-H), 0.88 (d, J = 6.5 Hz, 3 H, C26-H), 0.83 (s, 3H, C15-H or C16-H); ^{13}C NMR (125 MHz) δ 175.5 (C2), 165.5 (C31), 160.5 (C6), 150.9 (C14), 149.9 (C27), 139.1 (C13), 135.2 (C34), 130.1 (C5), 128.2 (C10 or C11), 127.8 (C29), 125.39 (C8), 125.36 (C28), 125.0 (C30), 123.9 (C10 or C11), 123.7 (C9 or C12), 116.5 (C35), 114.8 (C9 or C12), 77.1 (C17), 58.8 (C3), 56.4 (C7), 51.3 (C32), 50.6 (C22), 41.8 (C18), 40.7 (C4), 39.8 (C23), 34.3 (C20), 31.7 (C33), 31.4 (C19), 27.6 (C15 or C16), 26.6 (C21), 25.3 (C24 or C25), 23.4 (C15 or C16), 22.4 (C24 or C25), 21.7 (C26).



4.193

Aldehyde 4.193 (mp5-100). A solution of OsO_4 (a 2.5% wt, 41 μL, 0.003 mmol) in t-butyl alcohol was added to a solution of **4.200** (46 mg, 0.08 mmol) in dioxane (0.8 mL), H_20 (0.2 mL) containing 2,6-lutidine (38 μL, 0.03 mmol). $NaIO_4$ (140 mg, 0.66 mmol) was added, and the reaction was stirred at room temperature for 2 h, whereupon it was poured into a separatory funnel containing H_2O (10 mL) and was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with hexanes / EtOAc (4:1) to give 26 mg (57%) of **4.193** as a pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.64 (t, *J* = 1.5 Hz, 1 H), 7.71 (d, *J* = 7.9 Hz, 1 H), 7.32 (dd, *J* = 7.6, 0.9 Hz, 1 H), 7.30-7.26 (m, 1 H), 7.25-7.22 (comp, 2 H), 7.12 (td, *J* = 7.6, 1.0 Hz,1 H), 7.02-6.99 (comp, 2 H), 6.87-6.83 (m, 1 H), 5.10 (dt, *J* = 10.9, 4.7 Hz, 1 H), 3.76 (s, 3 H), 3.69 (dd, *J* = 16.3, 1.3 Hz, 1 H), 3.45 (dd, *J* = 16.3, 0.8 Hz, 1 H), 3.15 (d, *J* = 16.4 Hz, 1 H), 2.18 (d, *J* = 16.4 Hz, 1 H), 2.20-2.14 (m, 1 H), 1.97-1.92 (m, 1 H), 1.74 (dq, *J* = 13.7, 3.4 Hz, 1 H), 1.66-1.61 (m, 1 H), 1.52-1.43 (m, 1 H), 1.35 (s, 3H), 1.28-1.21 (m, 1 H), 1.25 (s, 3 H), 1.17-1.11 (m, 1 H), 0.98 (s, 3 H), 0.93-0.86 (m, 1 H), 0.88 (d, *J* = 6.5 Hz, 3 H), 0.81 (s, 3H); ^{13}C NMR (125 MHz) δ 197.7, 175.5, 165.2, 153.8, 150.9, 149.8, 139.2, 129.3, 128.6, 128.4, 127.8, 125.4, 125.0, 124.10, 124.08, 114.8, 58.8, 55.5, 51.6,

50.6, 42.1, 41.8, 40.6, 39.8, 34.3, 31.5, 27.8, 26.6, 25.1, 23.2, 21.9, 21.7; IR (neat) 2957, 1770, 1716, 1464, 1292, 1252 cm^{-1}; mass spectrum (CI) *m/z* 572.3008 [$C_{35}H_{42}NO_6$ (M+1) requires 572.3012], 403, 559, 570 (base M-1).

NMR Assignments. ^1H NMR (500 MHz, $CDCl_3$) δ 9.64 (t, *J* = 1.5 Hz, 1 H, C34-H), 7.71 (d, *J* = 7.9 Hz, 1 H, C9-H or C12-H), 7.32 (dd, *J* = 7.6, 0.9 Hz, 1 H, C9-H or C12-H), 7.30-7.26 (m, 1 H, C10-H or C11-H), 7.25-7.22 (comp, 2 H, C28-H), 7.12 (td, *J* = 7.6, 1.0 Hz,1 H, C10-H or C11-H), 7.02-6.99 (comp, 2 H, C29-H), 6.87-6.83 (m, 1 H, C30-H), 5.10 (dt, *J* = 10.9, 4.7 Hz, 1 H, C17-H), 3.76 (s, 3 H, C32-H), 3.69 (dd, *J* = 16.3, 1.3 Hz, 1 H, C33-H), 3.45 (dd, *J* = 16.3, 0.8 Hz, 1 H, C33-H), 3.15 (d, *J* = 16.4 Hz, 1 H, C4-H), 2.18 (d, *J* = 16.4 Hz, 1 H, C4-H), 2.20-2.14 (m, 1 H, C22-H), 1.97-1.92 (m, 1 H, C18-H), 1.74 (dq, *J* = 13.7, 3.4 Hz, 1 H, C21-H), 1.66-1.61 (m, 1 H, C20-H), 1.52-1.43 (m, 1 H, C19-H), 1.35 (s, 3H, C24-H or C25-H), 1.28-1.21 (m, 1 H, C18-H), 1.25 (s, 3 H, C15-H or C-16), 1.17-1.11 (m, 1 H, C21-H), 0.98 (s, 3 H, C24-H or C25-H), 0.93-0.86 (m, 1 H, C20-H), 0.88 (d, *J* = 6.5 Hz, 3 H, C26-H), 0.81 (s, 3H, C15-H or C16-H); ^{13}C NMR (125 MHz) δ 197.7 (C34), 175.5 (C2), 165.2 (C31), 153.8 (C6), 150.9 (C14), 149.8 (C27), 139.2 (C13), 129.3 (C5 or C8), 128.6 (C5 or C8), 128.4 (C10 or C11), 127.8 (C29), 125.4 (C28), 125.0 (C30), 124.10 (C10 or C11), 124.08 (C9 or C12), 114.8 (C9 or C12), 58.8 (C3), 55.5 (C7), 51.6 (C32), 50.6 (C22), 42.1 (C33), 41.8 (C18), 40.6 (C4), 39.8 (C23), 34.3 (C20), 31.5 (C19), 27.8 (C15 or C16), 26.6 (C21), 25.1 (C24 or C25), 23.2 (C15 or C16), 21.9 (C24 or C25), 21.7 (C26).

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Vita

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